CHAPTER VII

OBESITY

By EDWARD S. MILLS

Table of Contents

Introduction

Synonyms—Fatness, corpulency, adiposity pinguescence polysarcia lipomatosis universalis corpulencia morbosa are some of the synonyms

Definition—Obesity is the laying down of excessive deposits of fat throughout the body resulting from an intake of food beyond the caloric requirements of the body a positive energy balance

Historical Note—According to Immermann[1] the subject was discussed first by Hippocrates and later by Celsus and Galen For many years the prophylaxis of obesity was the only problem investigated, as it was not until the nineteenth century that Justus Liebig s work stimulated further investigation by such men as von Pettenkofer von Voit, Munk Ebstein Oertel and von Noorden all of whom have made valuable contributions to the subject The first modern dietetic regime was published by Banting[2] who was also the first patient so treated The opening sentence of his letter on Corpulence is of more than historical interest Of all the parasites that affect humanity I do not know of nor can I imagine any more distressing than that of obesity and having just emerged from a very long probation in this affliction I am desirous of circulating my humble knowledge and experience for the benefit of my fellow men with an earnest hope that it may lead to the same comfort and happiness I now feel under the extraordinary change—which might almost be termed miraculous had it not been accomplished by the most common sense means

Etiology

Predisposing Causes

Heredity—The role of heredity in predisposing to obesity still is debatable Older authors observed that obese patients gave a history of obesity in one or other parent in from 50 to 70 per cent of their cases[4, 5, 6] Indeed Anders made the statement that obesity depends more upon the peculiarity of the digestive and assimilative powers than upon the indolence of ancestors Such views are no longer tenable In none of the statistical studies have environmental influences been excluded as factors of prime importance There is sound experimental evidence, however to support the view that in certain animals there is a gene which predisposes to overindulgence in food thus producing obesity Dan

forth[87] was able to prove the presence of a gene in a yellow strain of wild mice which regularly produced obesity after sexual maturity, more marked in the female than in the male harboring the same gene The animals which became obese did so because of an increased consumption of food Heredity thus plays a dominant role in initiating the process A similar background may be present in some human cases of obesity Be this as it may the laying down of adipose tissue always is due to excessive food intake Whether this perverted appetite is due to a hereditary gene or environmental factors such as early training acquired habits of food selection or emotional disturbances must be determined in each individual case In most instances it will be found that environmental influences are much more important than heredity

Age—While sometimes occurring in childhood and adolescence obesity usually appears between the thirtieth and fiftieth year in the female and between the fortieth and the fiftieth year in the male In Dunlop and Murray Lyons's[3] series of 523 cases the age of onset was somewhat earlier In the female group 489 cases obesity began before the thirtieth year in over 40 per cent In the male group 34 cases overweight began before the fiftieth year In Fellows's study of 94 overweight individuals obesity developed in the males at a much earlier age

Sex—In the older reported series obesity was much more common in the female than in the male in proportions of over ten to one in some groups This inequality in the two sexes probably is much less evident at the present time due to changing environmental influences and the more vigorous physical activities of the female in the realms of sport and industry

Temperament Race and Climate—The phlegmatic individual with his emotional stability has been considered since the time of the Greeks to be predisposed to obesity The southern Italians the Dutch the Orientals especially the Hindu the South Pacific islanders certain African races and Eskimos are notoriously prone to obesity The predisposition has been assigned to their phlegmatic indolent and luxury loving temperaments such an explanation however is not applicable to the Eskimos or to the Hebrew race the women of whom also are prone to obesity The direct cause is to be found in an increased intake of food over and above their daily requirements

Occupation—The sedentary life requiring the minimum of muscular activity must predispose to corpulency thus the cook the butcher the barkeeper and the teamster usually are conspicuously fat

Previous Disease—Chronic diseases of the locomotor system as paralysis arthritis and varicose veins as well as anemia of various origins result in a sedentary life and hence decreased calory requirements. Further, disease of the respiratory and circulatory apparatus such as valvular heart disease, pulmonary emphysema and chronic bronchitis act in the same manner. Typhoid fever, pneumonia rheumatic fever, and other infections are followed frequently by a great increase in body weight for a similar reason.

Hormonal Dysfunction—It is recognized that certain types of hormonal dysfunction are invariably associated with obesity and this has led to such terms as hypothalamic obesity, dystrophia adiposogenitalis. Many women become obese after oophorectomy. Carefully controlled studies have shown, however, that neither ovary nor anterior pituitary has any specific effect upon fat metabolism. From a metabolic standpoint the laying down of fat in endocrine glandular dystrophies is no different from that which follows overeating. Hormonal changes may lead to lethargy and decreased calory requirements, to increased appetite or to both but they cannot compel the laying down of fat, if steps are taken to reduce the caloric intake to actual energy requirements. It is a simple problem of intake and output of energy.

Disturbances of internal secretion however may and do determine the site of the laying down of adipose tissue so that one can recognize a distribution of fat characteristic of certain abnormalities of the endocrine system. For this reason it has been the custom to classify obesity according to the associated hormonal dysfunction as for example, a pituitary type such as distrophia adiposo genitalis (Frohlich's syndrome) or Cushing's syndrome. In Cushing's syndrome for example there is obesity of the face and neck with loss of subcutaneous fat from the extremities. The result may be a normal or subnormal body weight yet the obesity of the upper part of the body is sufficient to suggest that the patient is overweight. Other examples of the effect of endocrine glands upon the distribution of fat are (1) the changes which occur in a sexually mature female who develops a virilizing tumor in the ovary and the restoration of form following its removal and (2) the different sites of deposition of fat in males and females if they become obese after puberty as compared with the laying down of fat before that event. Some of the endocrine disturbances which predispose to obesity are discussed under the heading of diagnosis.

Direct Causes

There is only one direct cause of obesity, the ingestion of more food each day than is required to meet the daily energy requirements, a positive energy balance, and this invariably results in storage in the form of fat.

It may be of interest to review a number of former misconceptions regarding the production of obesity. It is still a prevalent impression that *some persons gain weight even though they do not overeat, while others* fail to lose even though they are underfed. There is ample evidence to prove that the recognized laws governing energy exchange are not subject to variation within the human body. It is a common belief that many obese persons gain weight because of a *lowered basal metabolism*, but *this is contrary to the observations of Boothby and Sandiford*[103], Grafe[104] and others. Indeed, an obese person produces more heat than a normal person of corresponding age, height and sex, because the obese person has a larger surface area, and heat dissipation is a function of body surface. Therefore the heat produced by the fat person under basal conditions *is greater than that produced by* the normal individual under similar conditions.

Attempts have been made to explain obesity on the basis of diminished specific *dynamic effect of food*. A person who has been fed after remaining under basal conditions for some hours shortly will produce more heat than he did during the basal state. This specific dynamic effect of food is not caused by the process of digestion and absorption, since it will occur equally well after an intravenous injection of dextrose or aminoacids. *If this effect were reduced or wiped out, then the individual* might tend to gain weight on a calory intake below normal energy requirements. That this is not the case has been demonstrated by the experiments of Benedict and Carpenter[105] and Strang and McClugage[106].

Grafe maintained that the intensity of metabolism in the body is stimulated by overfeeding and depressed by meager *supplies of food*, in addition to the specific dynamic effect of the food. This he called *Luxuskonsumption*. Obesity or emaciation might result from abnormalities in this effect. Wiley and Newburgh[107] however failed to confirm Grafe's theory.

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of food, much below their basal requirements, fail to lose weight in the normal way. Newburgh and his associates[109] selected for study a group of patients with various types of obesity. These included obesity due to gluttony, hypothyroidism, pituitary dysfunction with low metabolic rate, a hypophysectomized woman weighing 295 lbs, a case of so called menopause obesity of 420 lbs, and a case of Dercum's disease. In no case was the total metabolism abnormal. None exhibited any capacity to live at a lesser expenditure of calories than normal persons. In those, who were active, the heat production was considerably greater than would be the case for normal persons of the same height, age, and sex, thus confirming Lauter's observations that such persons require more energy to perform a given piece of work than does the normal control.

How then can the apparent failure to lose weight on a sub basal diet in many obese persons be explained? Newburgh and his associates[109] have shown that although no weight loss may occur for a period up to 10 days, the actual weight loss over longer periods follows very closely the predicted values. They have shown that the apparent initial failure is purely a matter of water balance; that a temporary retention of water and salt accounts for the failure to lose weight during the initial period of the low calory diet.

The possibility that increased absorption of food might account for obesity in some persons has been investigated by Nenenschwander-Lemmer[110]. By comparing the combustible materials in the feces with those in the food he was able to show that obesity is not caused by an economy of food. The theory that adiposity is caused by a hereditary trait of the fat cells which enables them to accumulate fat that cannot then be released for fuel is no longer tenable. The fact that obese persons have more fat in the blood than normal when food is restricted suggests that they must be storing less or mobilizing more of it. Respiratory quotient studies on obese subjects after food and during the fasting state indicate that they are metabolizing more not less fat than normal controls.

In summary, it may be stated that in obesity more heat is produced during the basal state, more energy is required to perform a given piece of work, and the total heat production is greater than that of comparable normal persons. Since they are unable to absorb more energy from their food, they must eat more than normal people to avoid losing weight.

Chemistry, Physiology, and Pathogenesis

The fatty substances in the body may be classified in three groups

(1) the true fats and oils of the body mainly triglycerides of the fatty acids (2) the lipids combinations of fatty acids with nitrogen or with nitrogen and phosphorus substances which include phospholipids lecithin, cephalin and syringomyelin widely distributed and an important part of all cells in the body (3) cholesterol esters compounds of fatty acids with cholesterol a complex hydro aromatic secondary alcohol an essential constituent of all cells and fluids of the body Inasmuch as we are concerned only with obesity discussion will be limited largely to the first group into which falls the bulk of stored fat

The Triglycerides of Fatty Acids

The triglycerides of which the great bulk of stored fat is comprised are combinations of one molecule of glycerol with three of fatty acid *In neutral fat the principal fatty* acids are oleic acid ($C_{18}H_{34}O$) stearic acid ($C_{18}H_{36}O$) and palmitic acid ($C_{16}H_{32}O$) Oleic acid has a double bond in the middle of its fatty acid chain while the other two are completely saturated It is now considered likely that most of the glycerides comprising animal fats are mixtures of glycerides that they contain two or more different fatty acids in their molecule In addition to the oleic stearic and palmitic fractions the triglycerides also contain small amounts of more unsaturated acids such as linoleic and arachidonic acid The solidarity of animal fat depends upon the proportion of olein palmatin and stearin present Olein is a liquid fat with a melting point of 0 C while sterin and palmatin are solid below temperatures of 62 6 C and 69 3 C respectively

Absorption of Fat from the Gut

The view long held that fatty acids are absorbed as soaps no longer is tenable From the studies of Versar and his colleagues[70] it seems likely that fats are split first in the intestine into fatty acids and glycerine and are absorbed separately The fatty acids form a complex with bile salts which is water soluble and readily diffusable through the epithelial boundary after which it breaks down into fatty acid and once more combines with glycerin The bile salt then is returned to the liver via the portal blood stream

Blood Fat

The amount of fatty materials in the blood plasma varies but little during the postabsorptive state, although it may increase visibly following the ingestion of large amounts of fat such as olive oil or heavy cream. It exists in suspension in the form of minute particles called chylomicrons readily visible in dark field preparation of blood. The actual quantities of fats present in human blood during the postabsorptive state is listed by Boyd[69] as follows

Total lipid	0.589 mgm per 100 c.c. plasma
Total fatty acid	0.353
Neutral fat	0.154
Phospholipid	0.196
Free cholesterol	0.047
Cholesterol ester	0.19

After absorption about 40 per cent enters the portal blood stream while the remainder can be collected from the thoracic duct. The mode and transfer from epithelial cells to lacteals is unknown.

Disposition of Fat in the Blood.—According to Bloor two types of fat storage in the liver occur, (1) a temporary storage with a rapidly acting mechanism and (2) a more permanent one with a slower acting mechanism but with a greater capacity. The role of the liver in fat metabolism has aroused great interest. Leathes[70] studies first showed that the liver occupies an extremely important position in fat metabolism by preparing the fatty acid molecule for consumption in the tissues. It seems likely that the liver cells either selectively retain the more unsaturated fatty acids or change the saturated molecule into a less saturated compound. The ability of the liver to break down fatty acids into ketone bodies has been demonstrated by Embden and Kalberlah[71] and by Quastel and Wheatley[72]. There is evidence to support the view that the liver is the principal if not the only site of formation of ketones in the body. There is said to be a reciprocal relation between fat and the glycogen of the liver; when much glycogen is present there is little or no fat and vice versa, although this is challenged by the observations of Foster and Benninghoven[73]. The amount of blood fat may be increased readily by feeding certain articles of food, especially fat, sugar, and starches. Munk[74] first showed beyond a doubt that the transition of food fat into body fat occurs contrary to the opinion previously expressed by Ebstein[75]. This has been demonstrated again and again by feeding a

starved animal with an earmarked fat i e a fat of low melting point as olive oil or of high melting point as mutton fat and recovering it in the depot or tissue fats or the liver of the animal Von Liebig[6] was the first to demonstrate that the carbohydrates are the chief fat producers in the human organism rather than fat itself Von Pettenkofer[7] and von Voit[8] held that the action of carbohydrates in fat production was indirect that is to say their complete and ready conversion into carbon dioxide and water spares the fat of the food and the fat produced by the proteins from complete combustion and permits the fat to accumulate in the body The experimental evidence of Munk and Rubner[9] proves that the carbohydrates are capable of directly producing fats

Chaniewski[30] demonstrated that 86 7 per cent of the acquired fat originated in the carbohydrates It is believed by Rosenfeld[31] and emphasized by Richter[3] that this carbohydrate fat is chemically different being poorer in oleic acid *The method of alteration is complicated and involves a considerable alteration in the structure of the molecule the removal of oxygen and the fusion of several carbohydrate molecules into one molecule of fatty acid* This of course does not take place without some energy loss It was von Pettenkofer and von Voit who showed by experiments on dogs that it was probable that fat is formed from the decomposition of albumin or at least from a substance rich in carbon from which fat develops by synthesis The protein origin is supported by *the following facts (1) that the carbon of the albumin remains* behind as glycogen ( ) that fatty degeneration of the liver cells by autolysis occurs (3) that the fat of the milk in the nursing animal can be increased on a fat poor diet and (4) that whilst the urea which is excreted represents all the nitrogen which is thus passed through the body it represents much less carbon than is found in a quantity of the protein yielding the same amount of nitrogen This surplus of carbon, if not otherwise disposed of e g as carbon dioxide remains as a possible *source of fat to be deposited in the body* It must be admitted however that a direct fat production from albumin has not yet been shown although of course we know that albumin can be split into a carbohydrate portion which certainly can lead to fat formation

The storage of fat creates a tremendous reservoir of readily available *energy within the body The oxidation of each gram of fat gives rise to* 9 3 calories According to Carpenter and Fox[36] the respiratory quotient of the excess metabolism of subjects doing vigorous exercise depends on whether glucose is given before the experiment When no glucose is

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impulse and the area of cardiac dullness are masked by the overlying fat heart sounds at first are clear and distinctly audible but subsequently lose their force and are weakened by the overlying pads of fat Later cardiac decompensation may develop with paroxysmal dyspnea angina pectoris or general anasarca At first the pulse is full and strong later becoming weaker and of moderate frequency sometimes a *slight bradychardia* 50 to 60 per minute is noted

In many cases the obesity remains of a moderate degree but in others it increases to such an extent that the appearance of the patient becomes grotesque The features may become broad and fat the chin doubled or even trebled and the abdomen markedly pendulous In the Bushman and Hottentot women the cushions of fat over the tuber ischii the steatopygia may attain extraordinary proportions The body weight may be increased enormously the bodily movements are slow and clumsy the gait often is waddling heavy and hippopotamus like Later locomotion may become impossible owing to the great body weight and increasing muscular and cardiac weakness Cerebral hyperemia is the rule and is indicated by the throbbing of the carotids vertigo and tinnitus Some of this may come from an active carotid sinus reflex Epistaxis which is not uncommon may relieve it Cerebral hemorrhage may develop and usually ends fatally The marked *sweating predisposes* to intertrigo or eczema beneath the breasts in the abdominal folds and around the scrotum and labia *Pruritis* acne *rosacea* and alopecia are not uncommon The muscles are soft and flabby Cardiac insufficiency falling blood pressure and general anasarca may develop although hypertension is the more common Intercurrent diseases are badly borne

Special Symptoms

Cutaneous—The seborrhea and sweating which are found so commonly are due of course to an increased secretion of the sebaceous and sweat glands The sweating is a safety valve to counteract the prevention of the evaporation of heat by the non heat conducting adipose tissue As has been mentioned previously the sweating results in troublesome *intertrigo eczematous eruptions and great mental and bodily discomfort* Marked lineae atrophicae and venous and capillary ectasiae are observed *frequently Furunculosis and even carbuncles may develop*

Body Weight—It is of course impossible to fix exactly the weight at which *obesity begins* One can say however *that the standard weight* of a man of 5 feet 8 inches is 165 pounds one can say further that about

given the quotient is low indicating oxidation of fats (Anderson and Lusk[85] obtained similar results when they determined the respiratory quotient of starving dogs working a treadmill It would seem therefore, that the transfer of fat into energy takes place mainly during starvation or prolonged muscular exercise During rest and short periods of light exercise energy is derived from the oxidation of small molecules of carbohydrate protein and fat already in the circulation With the exhaustion of these the glycogen stores are drawn upon When these too are used up the fat stores are called upon to furnish energy and they do so directly and not as formerly believed, by conversion into carbohydrate

Morbid Anatomy

Normally the body fat stores are so well distributed as not to be obvious on casual examination Indeed, in the subcutaneous areas they contribute to the normal contours of the healthy body and within the body offer considerable structural support to such organs as the kidney pancreas, and spleen In the obese these stores become excessive In certain areas, such as the abdomen in the male and the breasts abdomen buttocks hips and thighs in the female the deposition may be out of proportion to that in other areas Fatty deposits also occur in the retroperitoneal tissues the mediastinum mesentery, omentum and pericardium The liver may be enlarged due to a fat vacuole in each liver cell Fatty infiltration of the heart muscle is rare according to Anders[37] unless the obesity is extreme

Symptomatology

Von Noorden[6] was the first to divide the symptoms into two groups the one group in perfect health but seeking advice because of restriction of mental and bodily activity or perhaps for aesthetic reasons the second group having complaints referable to the complications of the disease namely fatigue dyspnea backache weakness swelling of the legs arthritis of the knees or flat feet

Obesity often makes its appearance in youth or early manhood The complexion is usually although not always florid the sweat glands active The neck is thick and the abdomen prominent The cardiac

resulting in complete impotency In women there is enormous increase *in the size of the breasts Amenorrhea and sterility are common Pruritus* vulvae and leukorrhea often are troublesome symptoms

Nervous—There are often functional symptoms as headache muscae volitantes vertigo tinnitus and weakness Fearnsides[41] reported a case of a girl with obesity complicated by epileptiform attacks in whom there was no evidence of pituitary disease On the other hand cerebral arteriosclerosis and finally cerebral hemorrhage are all too frequent in the long standing or severe type of the disease

Osseous—Kirmisson[4] has reported six cases of obesity complicated by coxa vara of the familial type He believes that obesity can originate various osseous dystrophies and was the cause of the coxa vara in his cases

Metabolism—Observations on the basal metabolism in obesity have failed to establish any constant alterations in the fasting oxygen intake Magnus Levy[47] first showed a marked decrease in the oxidation process in cases of obesity Means[44] however using more modern methods in a study of 1 cases *of obesity concluded that the majority of obese sub* jects show no alteration in the basal metabolism as expressed in terms of their surface area even though obesity is of a most extreme type

One would expect that the nitrogen metabolism would show a definite retention in contrast to the nitrogen loss of emaciation Yet Richter[3] states the nitrogen balance is normal Dapper[48] has shown that marked weight loss can occur in obesity under proper treatment without a diminution in the nitrogen balance The uric acid metabolism may be disturbed in cases complicated by gout or nephrolithiasis In simple obesity however the urinary uric acid is not abnormal As has been noted previously gout is a frequently associated condition thus Anders noted gout in 43 per cent of his series of obesity While crystals of uric acid often are found in the urine there is usually no quantitative increase

The *carbohydrate mechanism* is injured in many cases *Allison*[49] examined the records of 121 cases of obesity and found that 17 showed glycosuria Sugar tolerance tests done on 20 of these including 8 with glycosuria showed diminished tolerance in all cases Of 12 cases of obesity examined by John 42 per cent had a positive tolerance test *Von Noorden believes that every* case of obesity should have a sugar tolerance test and given a reduced tolerance a true diabetes may be expected to develop later In obesity carbohydrate storage also is defective Krantz and Means[50] studied the metabolism in 7 obese patients

10 pounds additional weight can be carried for each 2 inches of additional height A weight above 250 pounds certainly is excessive, and anything above 300 may be considered as a marked obesity Gilman Thompson[39] mentions a male case of 410 pounds Anders heaviest case was 412 pounds but Duckworth[40] quotes a case of a male, 23 years of age, who weighed 448 pounds and eventually the incredible amount of 739 pounds

Circulatory —Obesity causes increased resistance in the blood vessels and thereby greater claims on the work of the heart Further, the intrathoracic deposits of fat offer a mechanical obstruction to the movements of the heart A vicious cycle thus is established as disease of the arteries and improper cardiac action predispose to obesity, and conversely Slight dyspnea on moderatae exertion often is the first warning that all is not well with the obese subject Marked breathlessness may develop subsequently as the result of myocardial weakness Finally, all the features of cardiac decompensation may present themselves such as general anasarca orthopnea cyanosis and pulmonary edema Arteriosclerosis with hypertension angina pectoris, cerebral anemia, and cerebral apoplexy are common manifestations of the advanced stage

Renal —Passive congestion from cardiac disease is the commonest renal manifestation, but a true chronic interstitial nephritis is by no means rare Further, there is a fairly high incidence of nephrolithiasis in obesity

Respiratory —Impairment of the pulmonary ventilation occurs from the accumulation of fat in the mediastinum and from the mechanical interference with the work of the intercostal muscles and diaphragm Hence the patient is subject to pulmonary edema, chronic bronchitis pulmonary emphysema and pneumonia Pulmonary tuberculosis is rare

Gastrointestinal —The appetite usually is good, sometimes though not commonly it is excessive periods of anorexia may occur The gastric juice and emptying time usually are normal though there may be a sense of fullness and even actual distension after meals Gastric hyperacidity may develop and more rarely peptic ulcer, chronic gastritis gastrectasis and even carcinoma Constipation is frequent often in association with hemorrhoids In some cases there is a tendency to diarrhea The liver may be enlarged and palpable due in part to fatty infiltration and in part to cardiac insufficiency Both may lead to a true cirrhosis Gallstones are apt to occur There are no pancreatic phenomena apart from diabetes and occasional pancreatic hemorrhage with fat necrosis in the peritoneum and the subperitoneal fat

Sexual —In men usually there is loss of desire and power of erection,

ment of distrophia adiposogenitalis (Frolich's syndrome) It has been shown by Rony and by others[8d, e] that administration of gonadotropic substances to patients with adipose genital dystrophy will not correct the obesity though it will induce genital development

In its fully developed state this glandular dysfunction is recognized readily Infantile or prepuberal cases may begin at any age before puberty It may result from an inherent defect of the hypothalamus *from tumors involving this area by pressure or displacement from trauma* to it or, more commonly from some infectious disease The subjects often are lethargic and sometimes of subnormal intelligence They usually have abnormally large appetites with a craving for sweets The degree of stunting of growth depends upon the age at which the disease begins Polyuria sometimes is a feature

In the adolescent or adult type males often are effeminate in disposition and appearance The distribution of fat and body hair is characteristically *feminine* In both sexes the *feet and hands are small* The fingers are slender and tapering with narrow pointed terminal phalanges As in the infantile type the sugar tolerance is increased Skiagrams of the head often will show thickening of the bones of the skull and rarely some abnormality in the pituitary fossa Other abnormalities are coxa vara genu valgum and *hypoplasia of the paranasal sinuses*

Clinically the glaring abnormalities of dystrophia adiposogenitalis are not always present and yet the careful observer will recognize a slight tendency in males to female distribution of fat and body hair a slight departure toward the pituitary type of hand and invariably some divergence of the tables of the skull from the normal Not infrequently inquiry into the family history of such cases will demonstrate that there is a strong hereditary tendency toward similar physical development *It would seem that such cases should be regarded as formes frustes* of this disorder

Laurence Biedl Moon Syndrome —The chief features of this disease are obesity polydactylism retinitis pigmentosa sexual infantilism mental deficiency and a family history of the disease or other mental defects *Degenerative* changes have been noted in the hypothalamic region at necropsy According to Sorsby and his co workers[13] slightly more than 100 cases have been reported in the literature The disease is thought to be due to some chromosome error such as a dislocation or a translocation leading to deranged gonadotropin production in addition to the developmental abnormalities

[illegible] on in a fasting period after the injection of epinephrin [illegible] mobilize carbohydrate The results show that in the obese there [illegible] glycogen supply with a greater tendency toward the [illegible] of fats as indicated by the low respiratory quotients obtained The glycosuria of obesity would seem therefore to be the result of a [illegible] to store carbohydrate as well as to oxidize it

Diagnosis

In the diagnosis of obesity it is important to differentiate the uncomplicated corpulent person from those in which there is some associated endocrine disorder Dunlop and Murray Lyon[7] found that 37 2 per cent of 525 cases were simple cases of overindulgence and the remainder mixed cases showing some type of glandular dysfunction The problem frequently is complicated by the involvement of several endocrine glands as for instance the pituitary and the gonads It seems fair to conclude, therefore that many cases of obesity have some associated endocrine disorder which calls for treatment in addition to the dietary restrictions necessary to reduce the body weight For this reason a few of the chief clinical and laboratory features of the endocrine disorders commonly associated with obesity are outlined

Hypothalamic Dysfunction—Pituitary Obesity —It would appear from animal experimentation on rats dogs and monkeys by a number of groups of investigators[88, 89, 90] that destructive lesions of the hypothalamus which sever descending nervous pathways from the paraventricular nuclei lead to the rapid development of obesity The animals eat more and are less active than controls but lose weight in exactly the same way as do the controls if given a diet below their calory requirements That no significant changes have occurred in the fundamental metabolic processes may be deduced from the following facts (a) the operated animals pair-fed with their controls behave, with regard to gain in weight like the controls (b) operated animals deprived of food lose weight at the expected rate and (c) oxygen consumption and R Q studies on such animals are normal Clinical cases of so called pituitary obesity are in reality instances of hypothalamic dysfunction since destructive lesions or extirpation of the pituitary gland without injury to the adjacent hypothalamic nuclei lead to emaciation and cachexia not obesity Dysfunction of hypothalamic centers is required for develop-

clinical evidence of myxedema may be lacking and the patients become truly obese

Pluriglandular Obesity—Adiposis dolorosa or Dercum's disease should be recognized readily by the presence of lipomata which are both painful and tender and by *the asthenia and psychic manifestations* It must be remembered that there are cases of so called Dercum's disease in which the fat is not localized in the form of tumors but generalized over entire regions or even over the whole body Conversely as Lyon[31] has pointed out many cases of simple obesity may present one or more of the symptoms of adiposis dolorosa but fall short of the typical picture of that affection as described

Lipomatosis—*Diffuse symmetric lipomatosis (adenolipomatosis)*, more common in men than women is characterized by the laying down *of nonencapsulated fatty masses in neck the shoulders arms and other* areas rich in lymphatic glands *Nodular circumscribed lipomatosis* is *common in women The fatty tumors are multiple and encapsulated* They are seldom tender and lead only to mechanical disability

Complications

Joslin is credited with the remark about shortening the waistline and lengthening the lifeline Longevity figures amply confirm this observation Life expectancy in overweight individuals of middle age as shown by actuarial tables varies with the degree of obesity Each 10 pounds of excess weight subtracts one year from the expected span of life

Diabetes Mellitus—The incidence of diabetes mellitus is high in obese individuals According to Joslin[80] from 70 to 85 per cent of persons with diabetes give a history of obesity Ogilvie[81] found that impaired carbohydrate tolerance in obesity is related to the duration and not the degree of corpulence Little tendency to diabetes occurred during the first 11 years of obesity but after 18 years every woman in his reported series showed diminished carbohydrate tolerance Later Newburgh and Conn[8] found that this tendency to diabetes disappeared after the individual's weight became normal and unrestricted diets could then be tolerated but the glycosuria tended to reappear with excessive gain in weight They suggested *that the condition is not true pancreatic diabetes* but due to an excessive accumulation of fat in the liver causing impairment of capacity to lay down glycogen at the normal rate

Pancreatic Obesity.—Organic hyperinsulinism of the chronic recurrent type may produce obesity by stimulating excessive ingestion of food to relieve the symptoms of hunger This is not true of functional hyperinsulinism as the symptom of hunger is transient Animal experiments tend to support these views[99, 100]

Hypogonad Obesity.—It is a popular belief that both men and women deprived of the gonads tend to become lazy and obese Statistics do not bear this out Rony has shown that, contrary to prevalent ideas women do not gain weight rapidly after the menopause Castration in man does not always result in obesity, and castrate lambs, goats, and rats gain no more weight than their controls on the same diet[101, 10]

Cushing's Syndrome.—Whether due to a basophil adenoma of the anterior lobe of the pituitary indirectly causing an increase in the adrenal cortical steroids or directly due to an adenoma of the adrenal cortex the clinical picture is similar Adipose tissue is laid down largely in the upper part of the body It has been called humpty dumpty disease' because of the striking obesity about the face, neck, shoulders, and upper chest These patients often show a protuberant abdomen but this is due to laxness of the abdominal walls and not to fat The increased appetite in this disease may represent an unsuccessful attempt at replacement of essential body proteins in the presence of a negative nitrogen balance with resultant positive energy balance and deposition of body fat[98]

If the disease develops in children puberty appears prematurely, and the secondary sex characters quickly appear Growth is rapid and the epiphyses fuse early In the adult female the voice deepens menstruation ceases the breasts atrophy and hair grows upon the face and body Homosexuality is a common feature Males, as a rule show fewer endocrine abnormalities although exaggeration of the masculine characters usually is observed No explanation of the peculiar distribution of the fat has been offered

Hypothyroid Obesity.—The reduction in basal heat production in hypothyroidism without change in appetite soon results in obesity provided the food intake is maintained Many classical cases of this disease are not obese however because appetite and consequent food consumption fall off correspondingly Much of the appearance of obesity may be due to myxedematous fluid which disappears rapidly once thyroid extract has restored metabolism to a reasonably normal level Myxedema may be recognized by the mental dullness the dry skin the coarse dry hair, the slow pulse and subnormal basal metabolic rate In other instances

clinical evidence of myxedema may be lacking and the patients become truly obese

Pluriglandular Obesity.—Adiposis dolorosa or Dercum's disease should be recognized readily by the presence of lipomata which are both painful and tender and by the asthenia and psychic manifestations It must be remembered that there are cases of so called Dercum's disease in which the fat is not localized in the form of tumors but generalized over entire regions or even over the whole body Conversely as Lyon[81] has pointed out many cases of simple obesity may present one or more of the symptoms of adiposis dolorosa but fall short of the typical picture of that affection as described

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[illegible] —Recent reports as to the frequency with which obese [illegible] hypertension tend to confirm the view, long held [illegible] of high blood pressure in this group is considerably [illegible] the normal person of the same age Short and Johnson[84] [illegible] 516 individuals applying for periodic health examina[illegible] in New York in order to determine the incidence of obesity and [illegible] In the group there were 2,856 overweight and only 658 normals When the two groups were compared, it was evident that obesity exerted a definitely positive influence in causing hypertension Less effect was noted on the systolic than on the diastolic pressure These authors are however inclined to the view that the incidence of hypertension in the overweight group is lower than is commonly reported

Body Build—Robinson and Brucer[83] have made the interesting observation that obesity is correlated with body build They found the incidence of obesity in broad chested men to be 37 per cent as compared with only 3 per cent in men with a long narrow chest If individuals in the latter group became obese hypertension invariably followed whereas no such correlation applied to the former

Cholelithiasis—The incidence of cholelithiasis is much higher in the obese than in the individual of normal weight Bauman[63] reported that 88 per cent of 215 patients operated on for gallstones at the Presbyterian Hospital of New York were overweight

Prognosis

The prognosis in simple obesity due to overindulgence in food is not good due to the difficulty of maintaing the patient on a subbasal diet over any prolonged period This is particularly true where overeating is due to psychological causes as in the case of the individual using obesity as a defensive weapon against undesired contacts or activities If these can be overcome and dietary restrictions are instituted before cardiovascular damage has occurred then the prognosis is excellent

In cases complicated by endocrine disorders the prognosis depends upon the nature of the disorder and not upon the degree of obesity Metabolically speaking it is no more difficult to bring about a restitution to normal weight in these than in the obese due to simple overindulgence in food

Treatment

The treatment of obesity is simple and at the same time difficult simple because it involves merely the creation of a negative energy balance by reducing the intake of food and increasing the expenditure of energy by exercise difficult because the obese hope to avoid restrictions in diet and added exercise They seek some magic elixir which will bring about a satisfactory reduction in weight without interfering with their daily habits of eating and drinking It is hardly necessary today to condemn the use of drugs on the one hand or to point out the futility of massage mineral baths etc on the other practices which have received support in the past but which have no place as substitutes for diet and exercise

Dietetic Treatment

The basis for all obesity diets is a reduction in the total number of calories maintaining the protein content however at a sufficiently high level to assure a nitrogen balance thus protecting the body proteins The reduction therefore is largely at the expense of the carbohydrate and fat Little attention need be paid to the F A G (fatty acid to glucose ratio) as there is little or no tendency to acidosis unless diabetes be an associated condition Obese patients on a low calorie diet are therefore not physiologically undernourished and this probably explains why acidosis as a rule does not occur Transformation of body fat to carbohydrate takes place readily[30] thus assuring an adequate supply of instantly available energy during muscular activity In this manner the body weight is reduced gradually through physiological methods

Since the days of J Harvey many dietetic regimes have been outlined Harvey s regime better known as the Banting diet was soon followed by the Oertel the Ebstein the Schweninger the Hirschfeld the Kisch and the von Noorden regimes The details of these diets which are now largely of historic interest are recorded in Table I

More recently Harrop[109] *suggested a milk and banana diet* which came into general use for a time The daily allotment was six large bananas and four glasses of skimmed milk totaling approximately 940 calories For prolonged use clear soup fruit vegetables and lean meat were added to bring the calorie value up to 1000 or 1 00 calories

TABLE I

Author	Grams Proteins	Grams Carbohydrate	Grams Fat	Grams Alcohol	Approximate Calories
Banting	172	81	8	(75)	1100 (1600)
Oertel					
Maximum	170	120	45	(60)	1600 (2000)
Minimum	156	75	25		1180
Ebstein	10	47	85	(0)	1300 (1450)
Hirschfeld					
Maximum	139	67	65		1400
Minimum	100	50	41		1000
Kisch					
Plethoric	160	80	11		1086
Anemic	200	100	12		1116
von Noorden	155	112	28		1366

The figures in parentheses in Table I include the calories from alcohol if this is administered

As has been emphasized already, the principle of all obesity diets is a reduction of the total calory intake to such a level that the fat stored in the body will be called upon to make up the daily energy requirements In the final analysis it would seem that it matters but little how this is accomplished so long as iron and vitamin intake is adequate, and there is sufficient protein to assure a nitrogen balance Usually 60 to 80 grams of protein is sufficient In practice it will be found that the greatest success in the dietary treatment of obesity lies in the regime which will least tempt the patient to transgress it This necessitates a careful analysis of individual tastes but it will often repay the labor involved and will permit of more drastic reduction in the total calories that could be accomplished otherwise

There is some evidence to support Oertel s contention that the food should be divided into small meals or portions Instead of three meals a day, five or six are recommended Frequent small feedings tend to dull the appetite and offset the pangs of hunger Water may be taken freely between the meals The following menu is of approximately 1000 calories It is adequate in protein and vitamins

Menu of Approximately 1000 Calories

Breakfast	Fruit One egg or slices bacon cooked crisp 1 slice toast 1 square butter (1 x 1 x 1/4) Coffee or tea with milk no sugar
Lunch	Clear Soup Fresh fruit or vegetable salad Fruit or fruit jelly Tea with milk or lemon no sugar
Tea	1 slice bread or toast or 2 crackers 1 square butter (1 x 1 x 1/4) Fruit Tea with milk or lemon no sugar
Dinner	Large serving meat fish or fowl Two green vegetables Fruit junket or water ice Coffee or tea with milk
Bed time	Fresh fruit or clear soup if desired

Note—All vegetables except corn and potato allowed All fresh fruits allowed When fruits are cooked no sugar should be added They may be sweetened by saccharine if desired Mayonnaise for use on salads should be prepared with mineral oil

Avoid All fried foods gravies sauces and soups thickened with flour cream soups fats and oils ice cream pork salmon mackerel sardines goose desserts made with eggs and cream cakes pastry hot breads and muffins rice honey jam syrups candy sugar and spaghetti

Mechanical Treatment

Oertel maintained that exercise should extend over at least 4 or 5 hours daily as he believed that fat as well as organic albumin was used up during muscular activity Lawrence[33] has shown that by far the greater percentage of one s total metabolism both at rest and during exercise is due to muscular activity for which carbohydrate alone is used Oertel s earlier views nevertheless are correct because further investigations[34] have demonstrated that both fat and protein

may be converted into carbohydrate, a chemical change probably necessary before these may be utilized by the muscles It thus becomes clear that muscular activity in the form of exercise is an important factor in the treatment of obesity

In prescribing exercises for the obese the following points should be given consideration The amount of exercise necessary to increase materially the negative energy balance is considerable Bedroom calisthenics night and morning are totally inadequate to supply the increased energy expenditure It should be the equivalent of 18 holes of golf per day a not inconsiderable physical exertion to one unaccustomed to it who is at the same time carrying from 60 to 100 pounds dead weight in the form of fat Such an effort often will result in symptoms of myocardial insufficiency or complaints referable to the back knees, or feet In such cases the loss of weight must be effected largely through dietary measures with a modified plan for special forms of exercise Riding is a useful form of exercise which puts little strain on the feet and one which is often popular

Hydrotherapy massage or a sojourn at some mineral spring may increase metabolism sufficiently to have a minor effect on obesity but in themselves they are useless It should be remembered that a large part of the reduction in weight which follows steam or hot water baths is due to a disturbance of water balance a loss of water and salt and does not represent an oxidation of body fat Such weight loss is likely to be replaced without delay due to the thirst which follows

Medical Treatment

Many years ago Oertel said that there is no such thing as the medicinal treatment of obesity but only the complications which require the administration of drugs Time has served only to emphasize the truth of this statement The drugs which have been employed as adjuncts to diet in the correction of the obese state may be divided into two groups —one which increases the metabolic rate and thereby increases the utilization of food within the body and the second which reduces the appetite and consequent consumption of food

Drugs in common use which increase the rate of consumption are thyroid extract and dinitrophenol The latter is mentioned only to be condemned It has no place in the treatment of obesity Thyroid extract is of value only where there is evidence of decreased thyroid

activity based either on metabolic or clinical evidence and it should be remembered in this connection that hypothyroidism is not synonymous with hypometabolism[111] Appetite depressant drugs commonly one of the amphetamines are widely prescribed in obesity By controlling the pangs of hunger they reduce the food intake They have the undesirable side effect of causing insomnia hence they should not be prescribed late in the day Instances of addiction have been reported[119] and one such in a physician has been observed by the author Amphetamine sulfate (benzedrine) reduces appetite at the price of both irritability and insomnia Deamphetamine sulfate (dexedrine) has fewer side effects and is hence a better drug It is given orally in doses of from 5 to 10 mg daily in divided doses The last dose should be given not later than mid afternoon because of its possible effect on sleep It should be remembered that the amphetamines are not without risk in the elderly and those with cardiovascular disease as they may cause minor elevations of blood pressure and metabolism It is of interest that Aldersberg and Mayer[11] treated 99 obese patients on diets alone and diets with thyroid extract or amphetamines They found that the result of diet alone were better than diet with thyroid and almost as good as diet with amphetamines Ipecac and digitalis once used to reduce appetite are no longer employed due to harmful side effects Reduction of food absorption in *the gut by purging has been suggested as treatment of obesity* Many patented remedies for the cure of obesity come under this heading They are usually some form of saline purgative The loss of weight which follows their use is mainly due to changes in water balance and not to oxidation of body fat

Summary

In the treatment of obesity of whatever type there is no substitute for a reduction in the caloric intake below the daily energy requirements If the expenditure of energy is increased by *well-controlled physical* exercises less reduction in diet naturally is required to produce the same weight loss The frequent failure of patients to lose weight on a greatly reduced diet due to water retention has been discussed already Such patients eventually diurese and the resultant weight loss is identical with the calculated values although the initial figures may diverge widely as shown by Newburgh and others

As a rule *the rapidity of the weight loss on a 1000 calory diet will*

may be converted into carbohydrate a chemical change probably necessary before these may be utilized by the muscles It thus becomes clear that muscular activity in the form of exercise is an important factor in the treatment of obesity

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vary with the degree of obesity The greater the initial weight, the more rapid the weight loss under treatment This is due to the greater energy requirements of the more obese individual as already explained in the section on etiology Contrary to expectation, patients in bed in hospital usually lose weight faster than those who are up and about This is due to the fact that few patients not under constant observation, can resist cheating from time to time The more exercise taken the greater the hunger and the greater the urge to gratify it When normal weight has been established the diet may be increased slightly without risk of a gain in weight because the need for burning up stored fat no longer exists Invariably when treatment is discontinued, patients become careless as regards their diet and a gradual gain in weight results A follow-up of 107 of the 5-3 cases studied by Dunlop and Murray Lyon[75] showed that the majority had put on weight gradually after discontinuing their strict regime They found that this tendency to regain weight was twice as rapid in the so-called endocrine cases

Symptomatic Treatment

The eczema and prurigo require dusting powders made from lycopodium or finely powdered starch to which benzoin, rose oil, and salicylic acid may be added

If precordial pain develops the patients activity must be restricted The use of vasodilators such as nitroglycerine, sodium nitrite, or amyl nitrite should not be used or should be prescribed with caution, if coronary thrombosis is suspected

For cardiac decompensation digitalis in some form is indicated Diuresis in these cases may be enhanced materially by following the course of digitalis with one of the mercurial diuretics

In anemic cases large doses of iron should be given preferably one of its ferrous salts such as ferrous sulfate gr v, three times daily

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PART I

THE PHYSIOLOGY AND CHEMISTRY OF LIPID METABOLISM

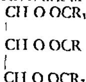
Clinical symptomatology of a disease can be understood only on the basis of a profound knowledge of the physiological functions of the organs involved in the disease. This conception of clinical medicine is especially true of diseases of the intermediary metabolism. A summary of the present knowledge of the chemistry and physiology of lipid substances is therefore an appropriate introduction to the group of diseases which are called lipoidoses or lipidoses.

A distinction formerly was made between fat and fat like substances which were classified as two separate groups. Glycerides of saturated and unsaturated fatty acids were placed in the first category. The second group called lipoids included the phosphatides cerebrosides ceramides sterols and derivatives of sterols. The term lipid has been introduced in the recent literature and is employed interchangeably for both groups. It will be used similarly in this discussion.

It is not the purpose of the author to analyze the disturbances of fat metabolism resulting in obesity or leanness. This discussion is to deal with the disturbances of the lipid metabolism only as they lead to the replacement of substances in the organ cells by lipids. Each one of the lipids may be predominant respectively in the pathological condition. If neutral fat is involved mainly the condition is referred to as fatty degeneration. In cases where a specific lipid is involved particularly the name of the lipid is used to designate the condition that is cholesterosis cerebrosidosis or sphingomyelinosis.

A PHYSIOLOGY OF FAT ABSORPTION

The general structure of fats is that of glycerol esters



We speak of neutral fats when all three alcoholic groups of glycerol are esterified with fatty acids (R_1 R or R) which may be either saturated or unsaturated. The palmitic stearic and oleic esters (C_1 and

(…) of glycerol prevail in human fats The unsaturated fats probably are intermediary products of the intracellular metabolism Fatty acids of higher carbon atom especially C[illegible] C[illegible] and C[illegible] are found also in the human organism These occur not so much as compounds of neutral fats but as esters of the phosphatide and cerebroside groups

Because the mechanism of absorption transportation deposition and synthesis of neutral fats depends upon so many factors it is not yet possible to present a precise scheme of the processes involved There has been a great diversity of opinion concerning fat absorption, which is considered one of the most important subjects in physiology[3] In the small intestine neutral fat is split into glycerol and fatty acids by lipases The bile may act as an emulsifying agent but the special role of the bile acids in the mechanism of the absorption of lipids has not been determined definitely (Verzar[6])

Verzar and his coworkers[56,57,58] demonstrated that the hydrophobic fatty acids which have resulted from the splitting of neutral fats in the intestine combine with the hydrophilic bile acids in the proportion of several molecules of fatty acids to one molecule of bile acid These two substances form a water soluble complex molecule which is taken up by the lipid mixture of the cell surface The fatty acids undergo absorption into the cells of the intestinal mucosa The bile salts on the other hand remain on the cell surface These can take up new fatty acids thus renewing the cycle of bile fatty acid combination and absorption of fatty acids In the intestinal mucosa the fatty acids are reesterified and delivered as neutral fats and phospholipids to the lymphatics These authors believe that the formation of glycerol phosphoric acid esters as intermediary products of fat absorption and fat resynthesis in the cell is one of the stages in this intracellular process

In contrast to Verzar's[6] lipolytic hypothesis of fat absorption is the theory of A L Frazer and his coworkers[81] suggesting that fats are only partly hydrolized in the intestines According to Frazer the unhydrolyzed portion is finely emulsified as a monoglyceride-bile salt-fatty acid complex and enters the intestinal cell as a finely dispersed emulsion Some of the fat is also split and absorbed as fatty acid The unhydrolyzed fraction passes mainly through the thoracic duct to the systemic circulation and the fat depots whereas most of the fatty acids pass directly to the liver via the portal vein Phosphorylation may play a part in the modification of the interfacial film of the unhydrolyzed fat globules

The effect of the adrenal cortex upon the phosphorylation of a

triglyceride as a part of fat resynthesis within the intestinal cell as assumed by Verzár is not confirmed[1] Schmidt Hershman and Thannhauser demonstrated[21] in recent experiments that glycerylphosphorylcholine is an intermediary metabolite of lipid metabolism in the intestinal cell while other phosphorylated compounds of fat metabolism did not become conspicuous The occurrence of glycerylphosphorylcholine in the intestinal mucosa furnishes a plausible suggestion that this substance acts as an acceptor of fatty acids Thus lecithin may be resynthesized or the fatty acids originated by digestion in the intestines may be transferred after esterification of this substance to glycerol for intracellular resynthesis of neutral fat (transesterification) The rapid incorporation of fatty acids even those foreign to the body like elaidic acid resulting from digestion of fats in the intestines[11, 1] would therefore be simply explained

It was believed formerly unsaturated fatty acids in neutral fats and phospholipids take up oxygen at the unsaturated bond and release it The unsaturated fatty acids were considered to act as oxygen transport agents within the cell In the light of the more recent conception of oxidation and reduction dehydrogenation is considered to be the mechanism of oxidation Dehydrogenases which are present in the cell take up hydrogen from saturated fatty acids and deliver it to a hydrogen acceptor It is therefore conceivable that unsaturated fatty acids may arise in this process

It is suggested also that the unsaturated fatty acids in neutral fats and phospholipids also may have an additional special purpose in the organism It has been shown that a lack of highly unsaturated fatty acids more than four double bonds can cause a deficiency disease in rats These animals were cured by the feeding of linoleic and arachidonic acids This disease so far has not been known to occur in man (Burr[6] Burr and Miller[7] Turpeinen[5])

The deposition and reabsorption of fat from the deposits in the tissue are influenced by enzymatic processes which are controlled by the nervous and endocrine systems of the organism It is not known what specific cells of the fat tissue are subject to nervous and endocrine control It is however erroneous to believe that the fat tissue is a changeless inert mass which is not affected by the general hormonal and nervous regulatory functions It is nevertheless possible that under pathological conditions these normal relations may be interrupted As a result the fat deposit may become disconnected and remain inert

B Disintegration of Fatty Acids in the Intermediary Metabolism

The intermediary disintegration of fat involves both the glycerol and fatty acid portions of the fat molecule[4] The glycerol part, 10 per cent, is burned to CO_2 and H_2O or is synthesized to sugar However, there is no definite proof at present that the fatty acid fraction is transformed into carbohydrate in the human organism

The oxidation of fatty acids is explained by two different theories The first is known as Knoop's rule of beta oxidation In this process the final CH_2COOH group is split off from the beta hydroxy-fatty acids as acetic acid and oxidized to CO_2 and H_2O This process is repeated until the whole fatty acid chain is oxidized The second process is known as the Verkaade omega-oxidation According to this theory the fatty acids may be oxidized on both ends to a di carbonic acid However, of the two processes that of beta oxidation is more important for the oxidation of fatty acids in the organism

At present no disease is known which involves the beta-oxidation of fatty acids If beta hydroxy butyric acid and ketobodies are demonstrable in the tissue fluids and excretions, it does not mean that fatty acids are not normally disintegrated but rather that the completion of the oxidation of acetoacetic acid must be achieved through the simultaneous disintegration of carbohydrates The appearance of these substances is therefore more indicative of a disturbance of carbohydrate disintegration than of faulty fatty acid metabolism

In the process of beta oxidation two carbon chains probably acetic acid originate continuously It was generally assumed that acetic acid then is oxidized to CO_2 and H_2O despite the fact that Embden (1908)[9, 9a] and Friedmann (1913)[1] had demonstrated in liver perfusion experiments that acetic acid may be resynthesized to acetoacetic acid It was not until 1934 that Monguio[8] in Thannhauser's laboratory demonstrated the significance of acetoacetic acid formation from acetic acid in the human organism Monguio injected sodium acetate intravenously into diabetic patients with the result of increased acetoacetic acid formation Experiments by the same author with liver slices of rats also revealed an increased acetoacetic acid synthesis after acetic acid as well as pyruvic acid were added thus proving that not only acetic acid but also pyruvic acid probably via acetic acid may lead to acetoacetic acid synthesis Acetoacetic acid therefore may originate not only from the katabolism of fatty acids from various sources but may be synthesized from two carbon fragments Ketosis i e acetoacetic acid formation

as a clinical symptom could no longer be attributed exclusively to katabolic disturbances of fatty acid metabolism For this reason the figures of ketogenic and antiketogenic metabolites as applied to diabetic diets have lost their arithmetical basis Jowett and Quastel[7, 7b] as well as Leloir and Munoz showed that acetic acid may originate from fatty acids with even or odd numbers thus increasing the sources of synthetic acetoacetic acid formation Weinhouse[?] carried the evidence of synthetic acetoacetic acid formation a step further He used in his vitro experiments octanoic and butyric acids containing radioactive carbon in the carbonyl groups and found that liver slices converted these substances into acetoacetic acid showing radioactivity in the beta keto group as well as in the terminal carbonyl group

It is believed that the ketobodies are formed from fatty acids by kata- and anabolism mainly in the liver However the liver has only a limited ability to oxidize the ketobodies further thus these substances diffuse into the blood stream and are carried to other organs Here especially in the kidney and muscles[7, 3b] the oxidation of ketobodies is completed yielding CO_2 and H_2O It is open to question whether or not such a diphasic mechanism of formation and complete oxidation of ketobodies is strictly divided between the liver on the one hand and the various organs on the other It is likely that the liver also may oxidize ketobodies at least to some degree and that the other organs may form acetoacetic acid in small quantities by ana and katabolism even if the main pathways of ketone bodies formation and oxidation show a diphasic direction

It was formerly believed that acetoacetic acid is directly oxidized in muscles kidneys and other organs to CO_2 and H_2O However it was found that another more complicated mechanism takes care of the acetic acid formed in the intermediary metabolism by a series of cyclic reactions Krebs and his coworkers [illegible] demonstrated that metabolites consisting of two carbon chains derived from carbohydrate metabolism (pyruvic acid ⟶ acetic acid) or acetic acid originating from fatty acid disintegration are ligated in the presence of oxalacetate with this substance forming cis aconitate i e a precursor of isocitrate Citric acid then undergoes a partial decomposition leading over alpha ketoglutaric → succinic → fumaric → malonic acid and to the reformation of oxaloacetic acid This cycle of reactions is accordingly referred to as the Krebs cycle or as the citric acid or tricarbonylic acid cycle Experiments with octanic acid in mashed liver suspensions demonstrated that the ligation of two carbon fragments with oxaloacetic acid for the

inauguration of the citric acid cycle is bound to the presence of oxaloacetic acid or to intermediary substances of the citric acid cycle. Oxaloacetate is primarily formed by CO_2 ligation to pyruvic acid. Pyruvic acid on one hand is mainly derived from carbohydrate metabolism. On the other hand oxaloacetic acid formed from pyruvic acid is necessary

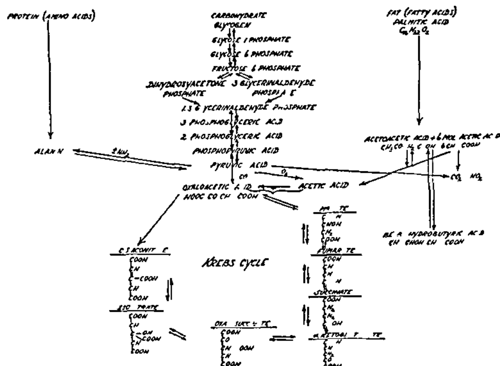


Fig. 1. Fatty acid metabolism and citric acid cycle (Krebs cycle) and its relation to protein and carbohydrate metabolism.

for the ligation of the two carbon chain fragments derived from fatty acid metabolism for citric acid formation. It seems therefore highly suggestive that the formation of oxaloacetic acid from pyruvic acid is the connecting point, i.e. the crossway between carbohydrate and fatty acid disintegration. Figure 1 displays the relation of the Krebs cycle to metabolites of the protein, carbohydrate and fat metabolism (see Fig. 1).

Enzymes of Disintegration of Neutral Fat—The enzymes involved in the disintegration and resynthesis of neutral fats are known as "esterases", lipase is the general term. These ferments are present in the organ cells. If they are found in the body fluids, especially the serum, it is probably the result of an overflow because these processes occur mostly intracellularly. It is not known to what extent every cell is qualified to split and rebuild fat. However, it should be assumed that the esterases are ubiquitous. The so-called fatty degeneration of a cell may be due to an unbalance of enzymes (esterases) within the cell. It has never been proven that the process of fatty degeneration is produced only by an external deposition of fat in the damaged cell. Fat phanerosis, the name coined by Virchow for a kind of fatty degeneration, may be the result of such an intracellular unbalance of enzymes concerned with fat metabolism.

If the blood plasma is milky it is called hyperlipemia (see section on Hyperlipemia). This appearance may be due to such factors as an increase of neutral fats, insufficient drainage of absorbed fats, increased fat transportation or pathological metabolic processes within certain organs. Fatty degeneration of an organ does not necessarily imply that there is a simultaneous increase of fat in the body fluids. Although hyperlipemia may be present with the fatty degeneration of some organs, it has not been observed in most of the diseases classified as "lipidoses". There may be also an increase of other lipids, like sterols or phosphatides, in the blood without any physical signs of hyperlipemia. It has been shown physiologically that there is an increase of neutral fat in the blood plasma after a fatty meal. A persistent hyperlipemia is, however, always a sign of abnormal processes in the body.

C. Classification of Lipids

The customary classification of the lipids into the groups of monoaminophosphatides (lecithins and cephalins), diaminophosphatides (sphingomyelins) and cerebrosides has to be modified in order to incorporate all lipids known at the present time. This classification originated at a period in which it was believed that the various members of each group differed from one another only in the nature of their component fatty acids. This assumption, however, holds only for the lecithins, whereas each one of the other groups includes individuals which differ also in the structures of their non fatty acid components.

from other individuals of the same group Furthermore some phosphatides of the acid fast bacteria do not fit into any group of the usual classification

The following scheme contains the lipids known at the present time

1) *Monoaminophosphatides* Fatty acid esters of a phosphorylated polyvalent alcohol combined with a nitrogen containing group Their ratio P N is 1 1 (Some monoaminophosphatides contain other organic groups in addition to those already mentioned)
   Lecithins Phosphoric acid diesters of diglycerides and choline
   Lysolecithins Phosphoric acid diesters of saturated monoglycerides and choline
   Cephalins All known cephalins contain their total nitrogen in form of a primary amino group (ethanolamine or serine)
   a) Phosphatidyl ethanolamines
      Phosphoric acid diesters of diglycerides and ethanolamine
   b) Phosphatidyl serines
      Hydrolysis products Fatty acids phosphoric acid polyvalent alcohols, serine
2) *Plasmalogens (Acetalphosphatides)* Phosphoric acid diesters of a fatty aldehyde acetal of glycerol and of enthanolamine
3) *Inositol-phosphatides* obtained from brain soybeans and bacteria
4) *Phosphatidic acids cardiolipids* Hydrolysis products Fatty acids polyvalent alcohols, phosphoric acids (bound as a monoester)
5) *Phosphatides of acid fast bacteria* Hydrolysis products Phosphoric acid polyhydroxy compounds (such as carbohydrates inositol) fatty acids with straight and branched chains
6) *Diaminophosphatides (Sphingomyelins)* Acid amides of sphingosine with fatty acids (ceramides) in ester linkage with phosphorylcholine
7) *Cerebrosides* Acid amides of fatty acids with sphingosine or dihydrosphingosine in glucoside linkage with galactose or glucose
8) *Cerebroside sulfuric acid esters*
9) *Gangliosides* Structure unknown hydrolysis products sphingosine neuraminic acid fatty acids and galactose or glucose

1 Phosphatides

The phosphatides are nitrogen and phosphorus containing lipids Phosphatides in which the atomic ratio of phosphorus to nitrogen is 1 1

are called monoaminophosphatides (lecithin and cephalin). Phosphatides in which the atomic ratio of phosphorus to nitrogen is 1 2, are called diaminophosphatides (sphingomyelin)[11]

a Monoaminophosphatides

The chemical constitution of the monoaminophosphatides is closely related to that of neutral fats. In both groups the lecithin and cephalin are respectively choline and cholamine phosphoric esters of the glycerides.

The most important difference between lecithin and cephalin is that the former has a quarternary ammonium base choline while the latter is esterified with ethanolamine. There is still some question as to whether natural lecithin contains choline as a quarternary base or as an intramolecular anhydride like betaine. On the other hand it has been established definitely that natural cephalin has a free amino group and that it is not an intramolecular anhydride.

The recent work of G. Folch[11] [11] [11] demonstrated that the lipid fraction usually obtained as cephalin consists of several different chemical substances, namely

(1) *Phosphatidylethanolamine* corresponding to the old cephalin formula printed above.

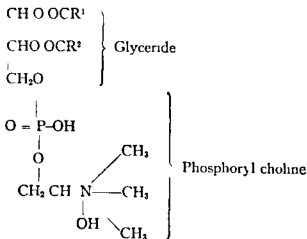
(2) *Phosphatidylserin* containing instead of ethanolamine the amino acide serin bound in ester linkage to phosphoric acid.

(3) *Inositolphosphatides*. In this compound apparently no N containing base like ethanolamine is preformed. Inositol is present as an inositol diphosphoric ester. The complete acid hydrolysis of the product yielded inositol, phosphoric acid, glycerol and fatty acids in ratios 1 1 1.

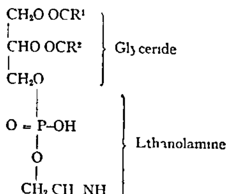
If one of the fatty acids in the lecithin molecule splits off, a substance remains which is called lyso lecithin. It is significant for its hemolytic property. The extent to which the lyso lecithins occur as normal or pathological intermediary products has not been established.

Lecithin and cephalin are unstable on exposure to light or oxygen. The degree of lability corresponds to their respective content of unsaturated fatty acids. The amount of lecithin in tissues usually parallels that of neutral fat. The amount of cephalin however does not correspond to that of neutral fat and lecithin. It has not been possible to isolate unsaturated lecithin or cephalin in crystalline form from organs. The

LECITHIN



CEPHALIN



following explanation may be given for the inability of unsaturated lecithins and cephalins to crystallize The various fatty acids composing the phospholipid molecules are so numerous that a great variety of lecithins and cephalins occur These substances differ in only one or two fatty acids Their physical properties are however so similar that the mixture does not crystallize A saturated lecithin (hydrolecithin) containing only palmitic acid (dipalmithylecithin) was isolated and crystallized from the lipid mixture of lung brain and spleen recently[11, 54]

The monoaminophosphatides and neutral fats differ in their physical properties As a result the principles governing the various processes

absorption transportation deposition and synthesis may be different also in both groups Since the monoaminophosphatides especially lecithin yield a fine watery emulsion absorption from the intestinal mucosa does not have to be preceded by a complete splitting[1] Lecithin and cephalin both are constituents of each cell The amount of lecithin and cephalin present in the various organs is different A partition of the cephalin fraction according to Folch[11] so far has been carried out only for the brain Lecithin is accumulated in proportion to the neutral fat The amount of cephalin depends on unknown factors While a high lecithin content may be found in fatty organs the cephalin content may at the same time be quite low

The quantity of cephalin in the serum and plasma is still questionable depending on the methods applied Thannhauser and his coworkers[13] as well as Artom[1] found measurable amounts of cephalin in the serum of humans and animals Folch and Van Slyke[16] found very little and Entenman and Chaikoff[9] almost none Up to now no one of the cephalins has been isolated from the serum by preparative methods

Intermediary Metabolism and Enzymatic Disintegration of Lecithin —Lecithin and cephalin are an integral part of the lipid mixture of which both the interior and the surface of the cell are composed Disintegration and synthesis constantly take place in this complex mixture[1] There is no doubt that the phosphatides are synthesized and disintegrated within the cell A specific intracellular *lecitholipase* leads to glycerylphosphorylcholine[21] as an important metabolite of the various lecithins Pancreatic lipase or duodenal juice are without effect on lecithin or cephalin

Lecithin is not split by alkaline phosphatase[21] Glycerylphosphorylcholine[21] is split very slowly while glycerophosphate is hydrolyzed very easily by alkaline phosphatase This behaviour is in contrast to the action of these substances toward acid hydrolysis in vitro Lecithin and especially glycerylphosphorylcholine are hydrolyzed quickly by normal hydrochloric acid at 30 C while glycerophosphate is highly resistant towards acids

In the last decade investigations on phospholipid metabolism were undertaken with radioactive phosphorus[7,10] as tracer substances Fishler Entenman Montgomery and Chaikoff[13] furnished strong evidence that the liver represents the only site of formation of the plasma phospholipids These authors administered radioactive sodium phosphate intraperitoneally to hepatectomized dogs It was found that the amounts of radioactive plasma phospholipids at several intervals up to 6 hours after

the injections were only very small in comparison to those found in the control animals Despite their inability to form plasma phosphatides, the hepatectomized animals were still capable of synthesizing phosphatides at a normal rate in kidney and intestines

Interesting new observations concerning the fate of the plasma phospholipids were obtained by Zilversmit Entenman Fishman and Chaikoff [1] and by Reinhardt Fishler and Chaikoff[2] The first group of investigators found in agreement with earlier observations by Hahn and Hevesy[1] that radioactive phospholipids when injected intravenously are rapidly and to a large part removed from the plasma The larger part of the injected plasma phospholipids could be recovered from various tissues such as liver spleen intestines kidney and red globules The second group of authors found that a portion of the radioactive phospholipids reaches the lymphatic channels and were found in the lymph of the thoracic duct The high rate of the passage of the phospholipids from the bloodstream through the tissues to the lymph channels and back to the bloodstream leaves no doubt that the phospholipids permeate the capillary membranes as such Since the phospholipids which passed into the thoracic duct are returned to the blood the observations discussed above establish the existence of a partial 'internal circulation of the phospholipids Apart from the physiological significance of the passage of the phospholipids through the capillaries it appears that the possibility of such an internal circulation must be generally considered in the interpretation of results obtained by the use of tracer substances in intact animals

Patterson Keevil and McHenry[28] found that in choline deficient rats the turnover of phospholipids was smaller than in normal animals These results substantiate the conclusions reached by Stetten and Grail[1 b] on the basis of phospholipid determinations in livers of choline deficient rats

As a general summary of the progress achieved in the physiology of phospholipids by the use of tagged molecules it can be said that tracer substances were used like tracer bullets in order to lighten the pathway and the location of the tagged substances in the organism However the studies with P_{32} have not so far contributed to our knowledge of the chemical mechanism of the intermediary metabolism of the phospholipids This will be accomplished only by the chemical isolation of the intermediary products

The different concepts of the physiology of the monoaminophosphatides may be summarized as follows

1 *Phospholipids are an integral part of the lipid mixture which comprises the body and the surface of the cell*

The amount of lecithin in the fat tissue as well as in other tissues except brain is greater than that of cephalin In the blood plasma only a very small quantity of cephalin is found

3 Monoaminophosphatides pass through the capillaries The degradation of lecithin in the intestinal mucosa and in other organs is produced by a specific lecitholipase The synthesis of lecithin is mainly effected by the liver

4 Unsaturated fatty acids in the lecithin and cephalin molecules formerly were considered to act as oxygen transport agents This opinion had to be revised in light of the more recent theory of oxidation and reduction by dehydrogenation

The increase of lecithin corresponds to that of neutral fats On the other hand the cephalin present in fatty organs is normal or even reduced

There is no disease known in which the lecithin or cephalin content of the organs is increased pathologically It was believed erroneously that the *monoaminophosphatides are accumulated in Niemann Pick's* disease The experiments of Klenk showed that only the diaminophosphatide is involved in the pathogenesis of this disease

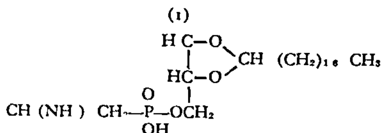
b *Plasmalogens (Acetal Phosphatides)*

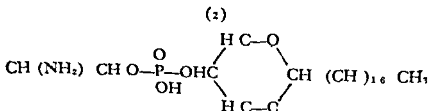
Plasmalogens — This group of phosphatides was discovered by Feulgen[illegible] during histochemical studies on the staining of tissues by fuchsin sulfurous acid This reagent which produces a purple color with aldehydes permits after treatment of the cells with sulfuric acid a selective staining of the chromatin structures of the nuclei due to the aldehyde groups appearing on hydrolysis of thymonucleic acid Feulgen introduced the term nucleal for his staining method He observed very soon that the staining effect of the nucleal reagent was not strictly limited to the cell nucleus but included in many tissues the cytoplasm although with a lesser intensity The staining of the cytoplasm was successful only in undefatted slices while that of the nuclei was not influenced by any treatment of the tissues with lipid solvents Feulgen concluded that different substances were responsible for the staining of nuclei and cytoplasma he proposed therefore for the unknown carriers of the fuchsin sulfurous acid staining in the cytoplasm the term plasmal Since he had already found in his earliest histochemical experiments that

the staining of the plasma was strongly accelerated and intensified by preliminary treatment of the tissue with acid or with mercuric chloride he postulated that the plasmal was not present in the cell as such but in the form of a hypothetical precursor which he designated as plasmalogen

Attempts to isolate plasmal and plasmalogen resulted in the observation that these substances were found exclusively in the phospholipid fractions of the investigated tissues On addition of a small amount of mercuric chloride to phospholipid suspensions from brain muscle or heart a strong plasmal reaction was immediately obtained Feulgen Imhauser and Behrens[11] were able to isolate the aldehyde from horse muscle phosphatides by steam distillation and subsequent condensation with semicarbazone as a crystallized semicarbazide and to demonstrate that this substance consisted chiefly of palmitic aldehyde semicarbazide contaminated with a small amount of stearic aldehyde semicarbazide An improved method for the preparation of plasmal semicarbazide from horsemeat has been reported by Behrens[1b] *

Structure of plasmalogen Feulgen and Bersin[11b] concluded from their observations that plasmalogens are acetals of fatty aldehydes with colamine glycerophosphate The structure of stearal plasmalogen would be represented by either of the following formulae





* Plasmalogen was isolated recently from brain by Thannhauser and Boncoddo (unpublished) The amount of plasmalogen present in brain is about 0 5 per cent of wet brain tissue and about 30 per cent of the total phosphatides in brain tissue

The assumption of an acetal linkage is supported by the stability of the nitrogen free group against alkali its sensitivity against acids and mercuric chloride

Plasmalogen can be determined colorimetrically on the basis of the test with Schiff s reagent[116, 11 ... 88c]

c Phosphatidic Acids

The term phosphatidic acid is used for substances which resemble the monophosphatides in their structure and composition but which differ from these lipins by the absence of nitrogenous constituents

Phosphatidic acids were discovered in cabbage leaves by Chibnall and Channon The free acids are soluble in organic solvents such as ether and acetone but very slightly soluble in water The sodium salts are soluble in water but insoluble in ether and very slightly soluble in cold alcohol The barium calcium and lead salts are insoluble in water but easily soluble in ether So far phosphatidic acids have been mainly found in plants

Plasmalogenic acid the phosphatidic acid of plasmalogen has been obtained by Feulgen and Bersin[33] after saponification of plasmalogen with hot sodium hydroxide

Pangborn[34] reported the isolation of a phosphatidic acid cardiolipin from beef heart Its presence seems to be essential for the complement binding activity of beef heart extracts with sera of syphilitic patients Cardiolipin alone has no complement fixing power but mixtures of cardiolipin cholesterol and lecithin resemble beef heart extracts prepared for diagnostic use in regard to their serological behavior

The separation of cardiolipin from lecithin was accomplished by the transformation into a barium salt which is insoluble in alcohol

d Diaminophosphatides (Sphingomyelins)

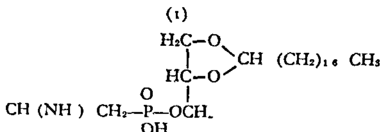
In contrast to the monoaminophosphatides which are glycerol esters and therefore related to neutral fat the diaminophosphatide sphingomyelin contains in its molecule the amino alcohol sphingosin instead of the alcohol glycerol Sphingosin present in the sphingomyelin molecule is partly a saturated and partly unsaturated sphingosin (Thannhauser and Boncoddo)[35, *] One of the two hydroxyl groups in the

the staining of the plasma was strongly accelerated and intensified by preliminary treatment of the tissue with acid or with mercuric chloride he postulated that the plasmal was not present in the cell as such but in the form of a hypothetical precursor which he designated as plasmalogen

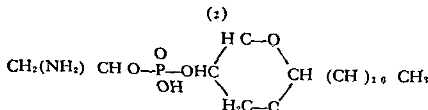
Attempts to isolate plasmal and plasmalogen resulted in the observation that these substances were found exclusively in the phospholipid fractions of the investigated tissues On addition of a small amount of mercuric chloride to phospholipid suspensions from brain muscle, or heart a strong plasmal reaction was immediately obtained Feulgen Imhauser and Behrens[11a] were able to isolate the aldehyde from horse muscle phosphatides by steam distillation and subsequent condensation with semicarbazone as a crystallized semicarbazide and to demonstrate that this substance consisted chiefly of palmitic aldehyde semicarbazide contaminated with a small amount of stearic aldehyde semicarbazide An improved method for the preparation of plasmal semicarbazide from horsemeat has been reported by Behrens[1b] *

Structure of plasmalogen Feulgen and Bersin[11b] concluded from their observations that plasmalogens are acetals of fatty aldehydes with colamine glycerophosphate The structure of stearyl plasmalogen would be represented by either of the following formulae

(1)



(2)



* Plasmalogen as isolated recently from brain by Thannhauser and Boncoddo (unpublished) The amount of plasmalogen present in brain is about 0.5 per cent of wet brain tissue and about 30 per cent of the total phosphatides in brain tissue

sphingomyelin in contrast to monoaminophosphatides should be insoluble in ether was erroneous since hydrolecithin a saturated monoaminophosphatide is also ether insoluble Pure sphingomyelin is yielded only after mild saponification of the ether insoluble lipid material as demonstrated by Thannhauser and coworkers[34, 36]

Sphingomyelin which crystallizes in needles is stable to light and oxygen It is less hydrophilic than lecithin It is also not as hydrophobic as cholesterol Because of its physical properties which place it in point of view of its water solubility between the monoaminophosphatides and sterols sphingomyelin may be assumed to play an important role in the lipid mixture which is present on the surface as well within the cell itself

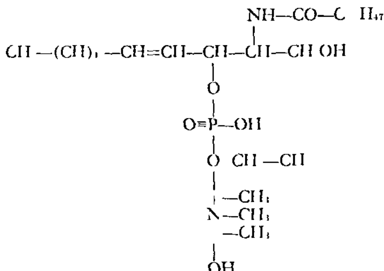
Sphingomyelin like the monoaminophosphatides is a constituent of the cell Under normal conditions the amount present in the cell is stable It does not depend upon such exogenous factors as nutrition or transportation of fat (Thannhauser Benotti and Reinstein[35]) There is probably an intracellular balance of enzymes controlling the processes of synthesis and disintegration Under pathological conditions however an unbalance of intracellular enzymes may lead to an accumulation or decrease of sphingomyelin within the cell

The following enzymes are concerned with the disintegration and synthesis of sphingomyelin phosphatases choline esterase and a ferment which splits and synthesizes the acid amide linkage of sphingosin and fatty acid Since purified alkaline intestinal phosphatase neither splits sphingomyelin nor lecithin[36b] it is suggested that the ferments concerned with sphingomyelin and lecithin disintegration are specific phosphatases

Experiments have been undertaken to hydrolyze sphingomyelin enzymatically with extracts of liver Lignoceryl sphingosin was isolated[4] Sphingomyelin is present in every organ cell According to the old conception sphingomyelin was related physiologically to the conduction of stimuli in the nervous substance Recent quantitative determination of the sphingomyelin content of brain and peripheral nerves demonstrated that the peripheral nerves are indeed many times richer in sphingomyelin than is the brain[35]

In Niemann Pick s disease an accumulation of sphingomyelin is found in the reticulum cells and histiocytes of almost all the organs In this disease the sphingomyelins are increased and retained only within the cell The body fluids especially the blood plasma do not contain a greater than normal amount of this substance This pathological condition within the cell is due to an unbalance of enzymes concerned

sphingomyelin molecule is esterified with cholin-phosphoric acid The other hydroxyl group occurs as free alcohol hydroxyl group The amino group of sphingosin is linked with a fatty acid by an acid amide linkage (—NH—CO—CH —), which is similar to a peptide linkage



It is evident from the recent work of Thannhauer and Boncoddo[11, 14] that the fatty acid constituents of brain sphingomyelin are different from those in visceral organs Pure sphingomyelin of brain after it is freed from hydrolecithin contains tetracosanic (lignoceric) acid ($C_{23}H_{47}COOH$) nervonic (unsaturated lignoceric) acid ($C_{23}H_{45}COOH$) and stearic acid ($C_{17}H_{35}COOH$) but no palmitic acid[11, 14] Pure sphingomyelin from visceral organs like lung and spleen contains only lignoceric and palmitic acid in about equal amount Klenk[1] reported that in sphingomyelin of brain of Niemann-Pick's disease only stearic acid is present as fatty acid component Thannhauser and Boncoddo found in sphingomyelin from Niemann-Pick brain mainly stearic acid but also nervonic acid[1, 4]

Because the monoaminophosphatides and diaminophosphatides both contain a basic group choline or cholamine as well as an acid group phosphoric acid these substances have the characteristics of a zwitter ion These features are definitely shown in the titration curve of Fischgold and Chain[13]

Preparation of Sphingomyelin —The preparative isolation of sphingomyelin has undergone revision The former conception[11] that only

1) The amount of amino nitrogen in phospholipid mixtures corresponds to the total amount of cephalins. The Van Slyke method is therefore widely used for the determination of cephalin in phospholipid mixtures. It must be emphasized however that unsaturated fatty acids evolve considerable amounts of inert gas with nitrous acid[111]. Folch, Schneider and Van Slyke[10, 111] found only very small amounts of cephalin in the serum lipids when they used the precaution of hydrogenating the lipids before the determination of the amino nitrogen. *Entenman and Chaikoff[8] obtained similar results by means of choline determinations in the plasma lipids.* It appears that amino nitrogen determinations in lipid mixtures should be carried out after the removal of the fatty acids by a suitable method of hydrolysis.

2) A micro method for the determination of the two known component nitrogen groups of cephalins, namely ethanolamine and serine, has been reported recently by Artom[1, 2]. It is based on the quantitative liberation of the nitrogen of either substance in the form of ammonia during the oxidation with periodate. When this method is combined with the quantitative separation of both substances by the selective adsorption of colamine on permutite, the amounts of either substance can be determined. In many tissues the sum of ethanolamine and serine as determined according to Artom's method agrees with the values for the total cephalin obtained by other methods. In some organs such as brain, kidney and lung the figures obtained with the periodate method are too high (probably due to the presence of sphingolipids in considerable amounts). It should be mentioned that Artom found considerable *amounts of cephalins in blood plasma, contrary to the results obtained* with some techniques already reported.

3) The sum of the choline containing phospholipids (lecithins and sphingomyelins) can be estimated by the determination of the choline obtained after refluxing the lipid mixture for hours with saturated *barium hydroxide[63]. The best method for the determination of choline* appears to be the spectrophotometry of its reineckate in acetone solution at 3 7mμ[53]. Amounts between 50 and 400γ can be determined with an error of 5 per cent.

4) The sum of the glycerol-containing phosphatides (lecithin and glycerol cephalins) is obtained by glycerol determinations in the dried phospholipid fractions according to Blix.

Attempts have been made to determine the glycerol in lipid extracts by periodate oxidation[8, 30a]. The application of this principle to the analysis of fats appears to give reliable results. In the case of phospholip

with the disintegration and synthesis of sphingomyelin (see scheme of cerebrosides in the following section)

e *Partition and Quantitative Estimation of Mono- and Diamino-phosphatides in Tissues and Serum*

The extraction of the wet tissue according to Bloor[3] is still the basis of the determination of the total lipins and of the individual lipin fractions This precedes all other analytical procedures For the determination of the total phospholipids the alcohol ether extract is evaporated to dryness under reduced pressure or in an atmosphere of N, the dry residue is extracted with a small amount of petroleum ether from which the phospholipids can be precipitated by acetone and magnesium chloride and determined oxydimetrically after treatment with chromic acid The author prefers to determine the total P directly in the petroleum ether extract because the results obtained with this technique are not influenced by the presence of cerebrosides Gortner[1] recently came likewise to the conclusion that the results obtained with P determination are more consistent than those obtained with the oxydimetric method

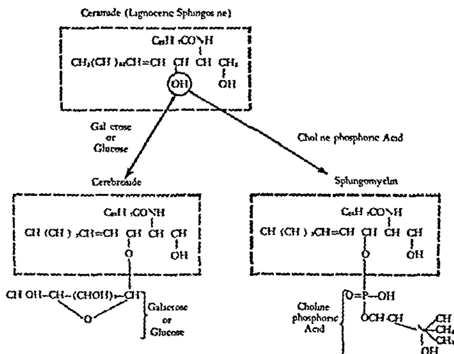
Folch and Van Slyke[14a] described a different extraction procedure for the plasma lipids by which certain disadvantages of Bloor's procedure (such as the contamination of the final petroleum ether extract with non lipid substances) can be avoided The lipids are precipitated together with the proteins by colloidal iron in the presence of magnesium sulfate Finally they are extracted from the washed precipitate by an alcohol ether mixture at room temperature

Various analytical procedures for the quantitative estimation of the individual phosphatide fractions have been devised When they are combined with the determination of the total phospholipids a fairly complete quantitative partition of a given phospholipid mixture is obtained It should be pointed out however that the results obtained with different schemes of the partition show some discrepancies which cannot be explained completely as yet One of the difficulties encountered in this field arises from the necessity of hydrolyzing the lipids prior to the chemical analysis Despite the fact that the general behavior of the lipins toward hydrolyzing agents is fairly well known the conditions required for quantitative hydrolysis of individual components of the various fractions have not as yet been studied sufficiently to exclude errors due to incomplete hydrolysis

pholipids in the serum usually is elevated In both groups of diseases, the ratio between the amount of cholesterol and phospholipids is not altered in comparison to that found in normal serum

2 Cerebrosides

Cerebrosides were found first in nervous tissue by Thudihum These substances are composed of a ceramide consisting of sphingosin bound to a high fatty acid in acid amide linkage The galactose or glucose is linked as a glucoside to the alcoholic hydroxyl group



The anabolism and katabolism of sphingomyelins and cerebrosides are interrelated intimately They both contain the same ceramide lignoceryl sphingosin as a constituent of the molecule The ceramide lignoceryl-sphingosin esterified with choline phosphoric acid yields sphingomyelin When it is linked with galactose in the glucoside linkage it yields the cerebroside, kerasin Therefore it may be understood that an accumula-

ids the use of periodate for the analysis of glycerol incurred serious difficulties: 1) the presence in the hydrolysate of interfering substances such as choline and serine and 2) the fact that the usual procedures for the hydrolysis of phospholipids do not lead to the liberation of glycerol as such but to the formation of a mixture of α and β glycerophosphoric acid; the latter does not react with periodate and thus escapes determination. It should be emphasized that α and β glycerophosphate rather than glycerol should be used as test substance whenever procedures for the determination of glycerol in phospholipid mixtures are to be checked.

5) The most convenient micro method for the quantitative partition of phospholipid mixtures into monoaminophosphatides and sphingomyelin has been developed by Schmidt, Benotti, Hershman and Thannhauser[41]. When lecithin or the cephalins are incubated with normal potassium hydroxide at 37° for 15 hours, the total amount of their phosphorus groups becomes soluble in dilute acids, while the phosphorus of sphingomyelin remains insoluble under these conditions.

6) A direct microdetermination of sphingomyelin as acetone insoluble reineckate has been described by Thannhauser, Benotti and Reinstein[49]. The sphingomyelin reineckate includes that of hydrolecithins which recently have been found to be present in several tissues such as brain and lung.[4]

It can easily be seen that by a suitable combination of several of the procedures just discussed, it will be possible to achieve a rather complete quantitative partition of the phospholipids. It must be emphasized, however, that the accuracy of figures obtained by difference should be carefully examined in each case. In the majority of tissues only the total lecithin and the total cephalin fractions are so large that errors of the individual determinations do not seriously interfere with the calculation of the differences.

Representative figures of the concentration of phospholipids in various tissues[1, 2, 3] and in isolated nuclei[1] have been reported by several authors.

Peters and Man[9, 10b] recently have reported their experiences concerning the amounts of blood phospholipids in humans under normal and pathological conditions. They found that the figures for the phospholipid P in normal serum range between 6.1 and 14.5 mgm. per 100 c.c. High values are often observed in thyroid deficiency and low values in hyperthyroidism although normal concentrations may be found in either condition. In patients with kidney diseases the concentration of phos

the carbohydrate components glucose instead of galactose (see Gaucher's disease) As a consequence of these results Klenk and Rennkamp [?] re investigated the cerebrosides of normal tissues and found that the cerebroside fractions of all organs examined contained very small amounts of glucose Thus there is little doubt that traces of glucosidocerebrosides may occur in normal cells

Cerebrosides are found chiefly in the nervous tissue With the exception of the brain other organs contain only small amounts sometimes even traces of cerebrosides Walz[?] reported that he found a small quantity of cerebrosides in the normal spleen This finding was confirmed by Thannhauser and Benotti[?] Some investigators have mentioned the presence of cerebrosides in the red blood cells Larger amounts have been reported in the blood plasma It is believed that the latter finding is erroneous since it is based on the fact that reducing substances are found in extracts with organ solvents of these organs after acid hydrolysis Thannhauser and Benotti working with one liter of serum could not isolate cerebrosides from plasma with preparative procedures

Bruckner [?] as well as Ottenstein Schmidt and Thannhauser [?] working with more sensitive methods confirmed the presence of cerebrosides in red blood cells but also was unable to find any cerebrosides in plasma or serum The latter authors [?] devised a method of estimation of galactosides and glucosides in tissues and serum Carter working with a lipid fraction of serum equivalent to about 200 liters of serum (obtained by E Cohn and coworkers in their electrophoretic fractionation of the serum) was able to isolate and identify minute amounts (about 100 mgm) of cerebrosides (personal communication from E Cohn)

The physiological significance of the cerebrosides is entirely unknown Occurrence of galactoside in the nervous tissue is thought to have a special purpose which may be related to the physical properties of the molecule or to the galactose itself Blix reported the isolation of a sulfuric ester of cerebrosides in which the sulfuric acid is esterified with the primary alcoholic hydroxyl group of the sugar The physiological significance of the esterification of cerebrosides with sulfuric acid has not been investigated

It is believed that a cerebrosidase i e a glucosidase is important as a ferment in the metabolism of cerebrosides However glucosidases like emulsin are not active on cerebrosides Thannhauser and Reichel demonstrated that cerebrosidase is almost inactive in the cells of the brain and spleen They showed also that it can be activated through the influence of cysteine and glutathione In recent experiments B Ottenstein

tion of cerebrosides or sphingomyelins within the cell may be the result of an unbalance of these enzymatic regulatory processes

The following scheme shows the relationship of ceramides to sphingomyelin and cerebrosides

The cerebrosides like the sphingomyelins differ among themselves in respect to the fatty acid which is linked with the amino group of the sphingosin Tetracosanic acid (lignoceric acid) nervonic acid and the lower fatty acids (palmitic and stearic) are found in sphingomyelin The ceramides contained in the cerebrosides are composed of high fatty acids derived from the C_{24} series (here again contaminated with small amounts of C and C_{16} acids) These fatty acids of the C_{24} series are lignoceric acid (tetracosanic acid) alpha hydroxy lignoceric acid (cerebronic acid) nervonic acid (unsaturated lignoceric acid) and oxynervonic acid (unsaturated cerebronic acid) These are present respectively in the cerebroside kerasin cerebrone nervone and oxynervone

Thierfelder and Klenk[54f] as well as Levene clarified the constitution of the fatty acids of the C_{24} series found in cerebrosides The location of the hydroxyl and amino groups in the sphingosin was discussed extensively by these authors Klenk believes that the amino group is the final group and that the hydroxyl groups are found in alpha beta position to the amino group

Carter and his associates[7], however found that benzoyl sphingosine does not react with periodate but forms a cyclic acetal with benzaldehyde in the presence of zinc chloride Since periodate is a specific oxidant for vicinal glycols and since 1 2 as well as 1 3 glycols form acetals it can be concluded that the two hydroxy groups of sphingosine are present in 1 3 position On the basis of these observations the structure of sphingosine can be expressed by the following formula



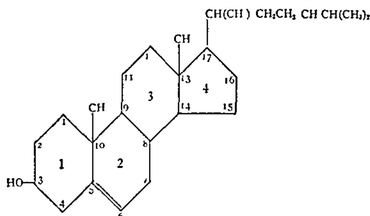
$$CH_3\ (CH\ )_1\quad CH\ CH\ CH(OH)\ CH(NH\ )\ CH\ OH$$

According to the customary definition cerebrosides are considered as galactosides of ceramides The individual cerebrosides were assumed to differ from each other only in respect to their fatty acid components This definition can no longer be considered adequate (1) Lesuk and Anderson[5e] isolated from the larvae of cysticercus fasciolaris dihydrophrenosine whose nitrogen-containing component is dihydrosphingosine Carter and Norris[b] found dihydrosphingosine among the hydrolysis products of cerebrosides prepared from beef brain and beef spinal cord (2) Several investigators[136 • 54] found that the cerebrosides which accumulated in the spleens of patients with Gaucher's disease contained

disease (infantile form of amaurotic idiocy) The normal cerebrosides in Tay Sachs disease are almost totally replaced by this fraction

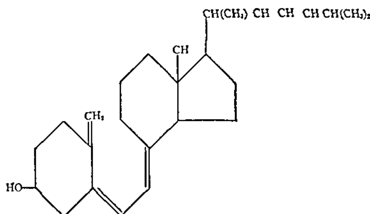
4 Cholesterol

Cholesterol was obtained first from gallstones by Poulletier de la Salle[59] in the eighteenth century The substance was given its present



CHOLESTEROL

name in 1816 by Chevreul[5] Windaus Wieland[60] Ruseiska[3b] and Rosenheim and King[7] gave us the current structural formula It has



VITAMIN D₂ (WINDAUS)

G Schmidt and S J Thannhauser[84] succeeded in demonstrating the presence of a cerebrosidase in pancreas

3 Gangliosides

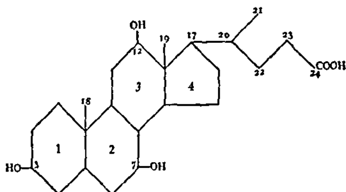
In brain the presence in tissues of a new group of phosphorus free carbohydrate-containing lipids the gangliosides was demonstrated by Klenk L Walz in 1927 described in beef brain and beef spleen a cerebroside fraction distinct from the known cerebrosides by the purple color of the Bial test and by its high sensitivity against acids This substance heated for a short time with sixteen per cent sulfuric acid formed a black flocculent precipitate of huminous substances Walz s observations on normal brain were confirmed later and extended by Blix who found that this cerebroside fraction gave a positive test for hexosamines with Ehrlich s dimethylaminobenzaldehyde reagent

In 1941 Klenk succeeded in isolating a hydrolysis product of the new cerebroside fraction in crystallized form This hydrolysis product for which Klenk introduced the name neuraminic acid represents the group responsible for the characteristic color reactions of the fraction and for its charring on treatment with dilute mineral acid According to the results of the elementary analysis the substance has either the formula $C_{11}H_{19}NO$ (molecular weight 281 16) or $C_{11}H_{21}NO_9$ (molecular weight 311 24) It titrates as a monobasic acid and contains its nitrogen in form of a primary amino group It is levorotatory in aqueous solution ($\alpha_D = -3491$) The substance decomposes at 200 without melting point It is easily soluble in water only little in methyl alcohol and insoluble in ethyl alcohol and ether

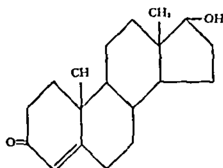
On being heated with dilute mineral acids the solution soon acquires a brown color During prolonged heating a black flocculent precipitate appears The substance however is stable against boiling at neutral or alkaline reaction

Neuraminic acid does not reduce alkaline copper solution It gives a positive ninhydrine test On boiling it with Bial s reagent an intense red color develops After heating it with Ehrlich s reagent in a paraffin bath of 140 a strong red color appears The test is strongly positive with 60% of the neuraminic acid

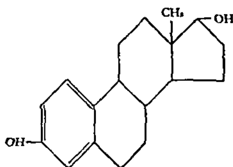
Klenk reported that relatively considerable amounts of similar substances could be found in the crude sphingomyelin fractions isolated from the brain in cases of Niemann Pick s disease According to Klenk very large amounts of this fraction accumulate in the brain in Tay-Sachs



Bile acid (cholic acid)



Testosterone (male sex hormone)



Estradiol (follicular hormone)

helped to clarify the conception of sterols and allied substances such as bile acids and sterol like hormones [1, 48, 4]

The relationship of the different sterols is understood best by a comparison of the formulae of the more important representatives of each group

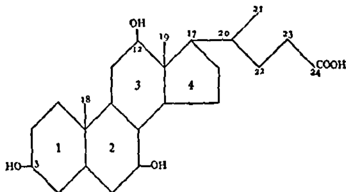
The cholesterol formula shows that the only double bond in the so called sterol skeleton cyclo pentanophenanthrane skeleton is in position 5 6 The hydroxyl group which is in position 3 makes cholesterol an alcohol Cholesterol may occur in the organism as free alcohol or as cholesterol ester The cholesterol esters found in the human organism are palmitic stearic and oleic esters

Derivatives of cholesterol which are the result of the special steric configuration of the molecule are present also in the organism When cholesterol is reduced in vitro by the addition of hydrogen atoms four different reduction products similarly are formed Two different steric configurations are possible on the dihydrocholesterol one of which is due to the position of the hydroxyl group in position 3 It is called epimerism

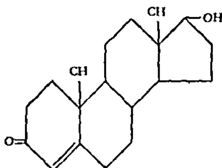
A cis'- and trans'-position of the hydrogen atom is possible in position 5 of the reduced sterols Coprosterol and epicoprosterol may be formed as a result These substances are distinguished from dihydrocholesterol and epidehydrocholesterol by the transposition of the hydrogen atom Coprosterol is found in the feces Dihydrocholesterol on the other hand is present only in the body fluids

The configuration of the bile acids shows that they are related to the coprosterol and not to the cholesterol series Bile acids are not formed from cholesterol in the liver because the organism apparently cannot change the cis- to the trans form (Thannhauser Jenke and Enderlen[50]) The experiments of Bloch [1] with deuterium containing cholesterol which seemed to prove the formation of bile acids from cholesterol are discussed in later pages of this chapter

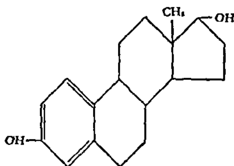
The ability of the organism to synthesize sterols has been investigated from many aspects Gamble and Blackfan[16] carried out balance experiments on infants on a milk diet They concluded that cholesterol is formed in the body because of the greater output than intake of the substance Thannhauser and his coworkers[48, 49] also obtained similar results in balance experiments on adults If the present knowledge based on the work of Schonheimer[37, 38] that plant sterols are not absorbed is applied to the figures obtained by Thannhauser and his coworkers[49b] the results are also in favor of a cholesterol synthesis in the human organism



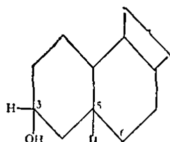
Bile acid (cholic acid)



Testosterone (male sex hormone)

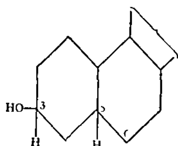


Estradiol (follicular hormone)

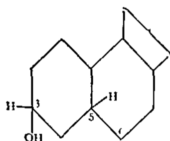


Dihydrocholesterol

epimerism of
dihydrocholesterol

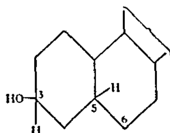


Epidihydrocholesterol



Coprosterol

cis trans
isomerism of
dihydrocholesterol



Epicoprosterol

Today the synthesis of sterols is demonstrated beyond doubt in many experiments such as in the incubation of eggs by laying hens[45, 9] Thannhauser Jenke and Enderlen[50] proved the synthesis of the sterol skeleton in dogs with bile fistulas These animals produced about two grams of bile acid daily regardless of the content of their food

Some investigators believe that the liver is the main organ of cholesterol synthesis This process probably occurs everywhere in the organism Low cholesterol values have been found in dogs after hepatectomy in patients with acute liver atrophy and in anemic patients with splenomegaly

The mechanism involved in the formation of cholesterol in the body is not known L Schindel[51] studying this problem experimented on dogs with bile fistulas These animal investigations however did not even show whether the proteins carbohydrates and fats in foods deliver the material from which the sterol skeleton is formed Macleod and Smedley MacLean [1] were the first to demonstrate that yeast is able to synthesize more than fifty per cent of its unsaponifiable matter (cholesterol) from acetic acid by labeling acetic acid with deuterium Schonheimer[39] fed materials containing deuterium to animals These studies showed that the small molecules of to 3 carbon atoms which may be derived from all three food constituents proteins, carbohydrates and fats are the building stones in the cholesterol synthesis He demonstrated also in similar experiments that bile acids are not formed from cholesterol but that they are synthesized in the body The same results had been obtained already by different methods in the experiments of Thannhauser Jenke and Enderlen [0] on dogs with bile fistulas

Bloch in more recent experiments with liver slices and acetic acid labeled with deuterium confirmed the findings of Macleod and Smedley-MacLean on yeast It was recently shown that cholesterol is also synthesized by surviving adrenal cortical tissue from acetate[4] The liver of animals synthesizes cholesterol from acetic acid which may be derived from fat carbohydrate or protein katabolism Whether all animal cells are capable of sterol synthesis is a question that cannot be answered definitely It is probable that every growing cell during maturation is capable of synthesizing cholesterol but this synthetic function seems to be maintained to a higher degree in recticulum cells and histiocytes in which the functional possibilities of embryonal cells especially of embryonal fat cells to form all kinds of lipids are preserved

While the synthesis of cholesterol in the body has been demonstrated by different experiments the process of fermentative disintegration or

the destruction of the sterol ring system in the intermediary metabolism has not yet been proven Balance experiments in which cholesterol and its derivatives are fed to mice merely indicate that this substance is retained and cannot be found again with digitonin precipitation or Liebermann-Burchard reaction Balance experiments have been carried out also on patients with essential xanthomatosis and high blood cholesterol[35] These studies show that about 20 grams of cholesterol disappear within seven weeks without being recovered in the stools While it would be plausible to explain this deficit as the result of disintegration in the intermediary metabolism no enzyme which can split the cholesterol skeleton has been found as yet in any organ

From the fact that the expected amount of cholesterol did not precipitate with digitonin it cannot be inferred that the cholesterol skeleton was destroyed in the intermediary metabolism The sterol nucleus may well be intact while slight oxidative or reductive changes may have resulted in a sterol unprecipitable with digitonin or not giving the Liebermann Burchard test Since it has been shown that bacteria present in the intestinal tract transform cholesterol to a sterol not precipitable by digitonin[14, 9] it may be concluded that the deficit of cholesterol in balance experiments in animals and in man is due rather to bacterial action in the intestines upon cholesterol than to a disintegration of the sterol ring in the intermediary metabolism The fission of the steroid molecule by soil bacteria was reported recently by Tuorfitt[45] and Tak[4d]

In any consideration of a disease where cholesterol is retained in the organism this question of the ability of the organism to destroy sterols is of great importance In the author s opinion destruction of the sterol skeleton in the intermediary metabolism cannot be accepted as a fact until the enzymes which should be involved in a disintegrating process are discovered

It is known by analogy that the animal organism can build up easily organic cyclic substances such as purines pyrols and indols the molecules of which are made up by a ring system but cannot disintegrate them subsequently On the other hand it is known also that bacteria can destroy such ring systems readily by fermentative disintegration As Ottenstein s experiments[8] suggest some kind of bacterial action may occur in the intestine in the case of cholesterol thus explaining the deficit in the balance experiments

As far as is known the changes which the human organism is able to make on the cholesterol molecule are few The following possibilities

will be discussed, (1) esterification (2) hydrogenation (3) bile acid formation (4) sex hormone formation and (5) vitamin D formation

The alcoholic hydroxyl which can be esterified with different fatty acids by means of an esterase may be split by reverse action The esterification of cholesterol changes its physical properties which not only have an influence on the absorption and transportation of this substance in the tissue fluids but are also important for the composition of the cell lipids A cholesterol esterase also seems to be present throughout the body The liver plays an important role in regulating the ratio of free cholesterol to cholesterol esters as it manifests itself in the serum of men and animals 70–75 per cent of the total cholesterol is normally present as cholesterol esters in the serum Schaber and Thannhauser[1] demonstrated that the esters are diminished in the serum in cases of parenchymatous liver disease especially hepatitis These findings were confirmed by many other investigators (Epstein and Lichtenstein[10 11])

Sperry[17] showed that incubation of normal serum increases the ester fraction of cholesterol He therefore assumed that normal blood contains a cholesterol esterase which may be responsible for maintaining the normal ratio of free cholesterol to cholesterol ester It is more probable that the cholesterol esterase which is found in organs especially the liver may be responsible for this ratio in the blood Willibald Klein[4] found that cholesterol esterase in the duodenum originates from pancreatic secretion He stated also that this esterase is not identical with other esterases This finding may be valuable for diagnostic purposes

Since dihydrocholesterol is found in normal human tissue and serum it is evident that small amounts of cholesterol are reduced on the 5 6 double bond in the intermediary metabolism The increase of cholesterol in the serum in essential xanthomatosis is accompanied by simultaneous increase of dihydrocholesterol (Schonheimer[3]) The presence of this substance suggests that a dehydrogenation and hydrogenation process occurs in the intermediary metabolism in which cholesterol and dihydrocholesterol play a part

The isomeric coprosterol on the other hand is not found in the tissues and does not take part in the intermediary metabolism Allocholesterol which is thought to be the unsaturated stereo isomeric sterol of coprosterol also is not present in the body It is therefore evident that coprosterol must originate from cholesterol only in the intestine It is believed that this transformation which must be accompanied by a change in the steric configuration on atom 5 is produced by the activity of bacteria In this process cholestenone is formed from cholesterol thus

leading to the coprosterol series (Schonheimer[29]) As long as cholestenone is not found definitely in the intermediary metabolism the transformation of cholesterol to the coprosterol series is not probable in the intermediary metabolism The fact should be accepted that coprosterol occurs only in the intestine

The bile acids have the same steric configuration as coprosterol Dogs with bile fistulas have shown an increased output of bile acids after injection with allocholesterol and coprosterol The daily amount of excreted bile acids in dogs which was as much as two grams a day must be even greater in human beings It is therefore evident that the formation of bile acids are not the result of a metabolic transformation of sterol already existing in the body but rather of a biological synthesis of the sterol skeleton in the liver (Thannhauser, Jenke and Enderlen[6]) In this synthesis the bile acids acquire the steric characteristics of the allocholesterol series Comparison with the usual cholesterol configuration shows that the marked difference is in the 5 position[8] Schonheimer and his coworkers[9], who fed deuterium containing cholesterol (deuterium added on the double bond) to animals did not find this isotope in the bile acid after feeding deutero cholesterol to dogs Bloch, Berg and Rittenberg[1] injected intravenously an emulsion of deuterium cholesterol in dogs which had an anastomosis of the gall bladder to the pelvis of the right kidney It was found that the choline acid in the urine of these dogs contained some deuterio cholic acid Most of the intravenously injected deuterio cholesterol, however, was trapped in the lung Such experiments with intravenous injection of deuterio cholesterol are not convincing as long as the sterol substances of the intermediate metabolism are not isolated thus proving the epimerization of the cholesterol molecule to the sterol from which cholic acid is derived

Tagging large molecules like cholesterol with deuterium to demonstrate various and complicated changes within a large molecule is ambiguous It seems for the time being that the experiments of Thannhauser and coworkers[6, 7] showing that 2 to 3 grams of bile acid daily are produced in the liver by synthesis are consistent with the physiological concepts in contrast to the idea that 2 to 3 grams of cholesterol are first synthesized in the liver and metabolized afterwards to bile acids by changing the cis and trans position in the sterol molecule in an unprecedented way It seems however most doubtful whether this transformation of cholesterol to bile acid takes place in the organism as the main pathway for the formation of bile acids

Although it is known that the male and female sex hormones as well

as the hormones of the adrenal cortex are sterols[31] the origin of these substances has not yet been determined definitely The formula shows that there is a sterol nucleus in the male sex hormone[17] In the female sex hormone the ring I has three double bonds which are characteristic of a benzene ring The side chain of the cholesterol molecule is missing in both these substances Because of the fact that the ring system is intact and the changes are mainly in the side chain and on the OH groups it may be possible that these substances originate from the disintegration of cholesterol in the intermediary metabolism An alternative explanation also has been advanced It is believed that there is an independent synthesis of sterols in the sex organs themselves The hypothesis for the second process seems more probable than the first because of the fact that such extensive changes on the side chains of cholesterol are hardly likely to occur

It was believed erroneously that the formation of vitamin D irradiated ergosterol in the organism may be due to the changes made in the cholesterol molecule in the intermediary metabolism Windaus[6] demonstrated that artificial or natural irradiation breaks up ring II in the sterol skeleton Although it is not known whether an enzyme which can perform a similar function exists in the organism it must be assumed that light and irradiation can do what the organism itself cannot do The small quantities of ergosterol which are absorbed in contrast to other plant sterols are however transformed in the organism into vitamin D by artificial or natural irradiation The slow absorption and transformation of only small amounts of ergosterol by irradiation in the skin may be assumed to be protective factors against hypervitaminosis D[3] Tachysterol is an intermediary product which originates from irradiation of ergosterol

Cholesterol Absorption —An important problem of cholesterol metabolism concerns the kind of sterols absorbed in the human and animal organism Schonheimer and his coworkers[3 36] showed that neither herbivorous nor carnivorous animals absorb plant sterols from the intestines Only small amounts of ergosterol are absorbed Although dihydrocholesterol is formed in the intermediary metabolism and excreted in the intestines it is not reabsorbed Animal cholesterol is the only animal sterol undergoing absorption from the intestine

The mechanism of the selective absorption of sterols has not been explained yet It is of great importance however for the sterol metabolism protecting the body against an accumulation of sterols The synthesis of cholesterol in the metabolism prevents a deficiency of

leading to the coprosterol series (Schonheimer[39]) As long as cholestenone is not found definitely in the intermediary metabolism the transformation of cholesterol to the coprosterol series is not probable in the intermediary metabolism The fact should be accepted that coprosterol occurs only in the intestine

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Although it is known that the male and female sex hormones as well

izes hemolytic substances such as saponins different glycosides and animal venoms To accomplish this the double bond and the hydroxyl group in the sterol molecule must be available Esters and saturated sterols exhibit no anti hemolytic effect

In a similar way cholesterol is supposed to be effective against some of the bacterial toxins This concept is based on its action in vitro against tetanus toxin Furthermore it is observed that in most febrile infectious diseases blood cholesterol is reduced at the climax and also in the terminal stages Cholesterol forms insoluble addition products with anti hemolytic substances like tetanus toxin in vitro but most of these substances or reactions occur neither in normal nor in the diseased body The claim then that the main function of cholesterol must be a detoxifying one has not yet been satisfactorily proven

Hypotheses referring to the function of cholesterol are as numerous as they are questionable so that the mention of a new hypothesis may be superfluous The presence however of dihydrocholesterol in the tissues as discovered by Schonheimer may be explained by the assumption that there is an oxidation reduction system in the intermediary metabolism within which cholesterol dihydrocholesterol plays a role similar to that which succinic and fumaric acids play in an already known system of this kind

The cells of the body break down and are rebuilt In this process cholesterol becomes available and is needed Cholesterol is synthesized excreted and accompanies neutral fat wherever fat is transported and deposited in the body The concentration of cholesterol in the serum therefore depends on different factors so that an increase or decrease of cholesterol and cholesterol esters in the serum is not due to a uniform cause

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cholesterol in the organism due to an unsatisfactory absorption Diseases thus may originate from an accumulation of cholesterol due to an unsatisfactory excretion (see Pathology of Xanthomatous Diseases)

The amount of cholesterol excreted in the bile of dogs with bile fistulas in comparison with the amount present in the feces of these animals demonstrates that a good part of the cholesterol is excreted directly by the intestine In the human organism there is apparently no direct excretion in the intestines of sterols which are derivatives of the sex hormones or which are vitamins As far as it is known these sterols seem to be excreted only in the bile Pathological conditions may arise thus through retention or inactivation of sterol hormones in patients suffering from total obstruction of the bile duct A condition is observed which results in gynaikomastic in males by retention of female sex hormones in chronic obstructive jaundice Knowledge in this respect is meager The advancement of quantitative methods no doubt will enlarge this new field of physio pathology of sterols

The ability of the intestines to excrete cholesterol is not the same in all animals The herbivorous animals cannot excrete cholesterol as quickly as carnivorous animals There are experiments which even demonstrate that herbivorous animals excrete almost no cholesterol Yet herbivores can absorb animal sterol very readily Therefore atheromatosis can be produced experimentally by feeding these animals cholesterol (Hueck[1] Leary[6])

In summarizing it may be assumed that cholesterol is absorbed and synthesized in the metabolic processes and that it is excreted as cholesterol in the bile and intestines In the intestines cholesterol is transformed for the most part into coprosterol It may undergo a bacterial disintegration in the intestines to an unknown extent

The function of cholesterol itself in the metabolism is rather doubtful although its wide occurrence in the animal kingdom is supposed to give some indication of its necessity The main function of cholesterol may be indicated in the fact that cholesterol and cholesterol esters are present in a constant percentage *in every lipid mixture occurring on the* surface or within the cell As already mentioned cholesterol is a hydrophobic colloid in contrast to the hydrophilic monoaminophosphatides The author believes that the correct mixture of the lipids in the cell depends on the presence of an adequate amount of cholesterol One of the most important functions of cholesterol thus is seen to result from its physical properties

Some authors attach significance to the fact that cholesterol neutral-

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PART II

HYPERLIPEMIA

Introduction and Definition

The following lipid substances are found in the serum: neutral fat, lecithin, cholesterol and cholesterol esters, sphingomyelin and traces of cephalin (see Table I). The cerebrosides are not present in measurable quantities in the serum or plasma. The red blood corpuscles, however, contain small amounts 0 per cent. The cerebrosides usually remain in the cells where they are built.

TABLE I

Normal figures of serum lipids (fasting)

Total lipids	400–700 mgm %	
Total fatty acids	190–450	
Fatty acids derived from neutral fat	0– 00	
Neutral fat*	0– 00	
Total cholesterol	150– 60	
Free cholesterol#	30– 35	
Ester cholesterol	70– 75	of total cholesterol
Total lipid phosphorus	6– 10 mgm %	
Total phospholipid	150– 50	
Sphingomyelin	10– 30	
Saponifiable phospholipids (lecithin and cephalin)	110– 30	"
Cephalin	0– 20	
Lecithin	150– 30	"

The designation *hyperlipemia* should be reserved exclusively for an abnormal increase of neutral fat in the serum. The terms *hyperlecithemia* and *hypercholesteremia* should be used for the increase of these respective lipids in the serum. Hyperlipemia usually is accompanied by hypercholesteremia and hyperlecithemia, whereas the latter conditions occur

* Calculated according to the formula of Thannhauser and Reinstein[5]

\# Ratio free cholesterol: cholesterolester 1 : 2.7

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increases but not proportionately with the neutral fat The values in the literature for lecithin comprise all the phospholipids The inclusion of the values for sphingomyelin and cephalin in the lecithin figure has been due to the fact that there was no method for determining each of these three substances separately Thannhauser Benotti and Reinstein revealed by their method of separating these three phospholipids that cephalin and sphingomyelin do not accompany the increase of neutral fat and lecithin in the serum On the contrary in very severe hyperlipemias the cephalin value has been found low and the sphingomyelin value normal These findings were confirmed by the newer methods of lipid partition in the serum (see Table I) Only the figures for the cephalin content in the serum were found as already mentioned to be even lower if cephalin was present at all

Normal figures of enzymes in the serum

Esterase		
Monobutyrin	6–9	units
Tributyrin	–3	
Lipase	0–0 7	
Phosphatase (alkaline) Bodansky units	1–4	"
Amylase	–4	

The level of lipid substances in the serum is influenced by the different conditions under which fat metabolism takes place The amount of lipid substances in the serum is dependent upon the following factors (1) the absorption of fat from the intestines ( ) the migration of fat from fat depots to the organs of fat disintegration (3) the deposition of fat in subcutaneous and other fat storing tissue (4) the speed of fat disintegration in the organs that is the balance between fat transportation and fat combustion and (5) the disturbance of the lipid metabolism within the cell

Hyperlipemia may result as a clinical symptom from a disturbance of any one of these five processes However it is obvious that the symptom is of diagnostic value only if its origin can be traced

1 Alimentary Hyperlipemia

J Levy[3] working with H Strauss was the first to attempt a diagnostic study of alimentary hyperlipemia This author upon microscopic

without hyperlipemia in essential xanthomatosis of the hypercholesteremic type as well as in xanthomatous biliary cirrhosis (see sections on these diseases).

The serum is the medium for the transport of these substances. After absorption from the intestines the bulk of lipids is supplied in the form of neutral fat and monoaminophosphatides to the blood stream by the way of the thoracic duct[1]. It is important to note that only a minor part of the fat is absorbed by the vessels of the portal system and transported directly to the liver. The amount varies with the time of food absorption[5, 6, 8, 13, 40]. Cholesterol, cholesterol esters and especially sphingomyelin show more constant values in the serum, because they do not depend so much upon the intestinal absorption as upon the cellular metabolism of organs and tissues.

Fat splitting enzymes, which are able to split glycerol ester as well as esters of other alcohols with fatty acids, are found also in the serum. These enzymes are esterases, mono-, di- and tri-esterases. The latter is known as lipase. The concentration of these enzymes in the serum is not sufficient to cause disintegration in the blood stream to any large extent. The amount of these enzymes, as well as their activity, is an indication of the enzymatic activity in the organs of fat metabolism, fat deposition and fat disintegration. Since fat disintegration does not take place in the blood, an accumulation of lipid substances in the serum is not the result of an insufficient enzymatic action in the blood stream.

The serum also contains alkaline and acid phosphatase. Neither of these phosphatases splits phosphatides[5]. At present it is not known whether the specific enzymes concerned with the phosphatide disintegration, like lecitholipase, occur in the serum. Since lecitholipase is an intracellular enzyme, it is more likely that the specific enzymes for phospholipid metabolism are found in the organ cells rather than the serum.

Hyperlipemia usually is recognized by the milky, opaque appearance of the serum (sanguis albus seu lacteus). The serum, however, is not milky in slight stages of hyperlipemia, where an increase of 50 to 150 per cent of the normal value is found. Although the physico-chemical conditions resulting in marked hyperlipemia cannot be discussed here, it should be recognized that an increase of fat up to 100 per cent of the normal value may exist without a definite change in the appearance of the serum. Only chemical analysis can justify the statement that the lipid content of the serum is within normal range.

The milky appearance of the serum is the result of an increase of neutral fat. Lecithin, which generally accompanies the neutral fat

Wechsler[47] studied 67 patients free from hepatic or pancreatic disease after the ingestion of olive oil He reported that 63 per cent had a more or less marked increase of blood fats 17 per cent had no increase and 19 per cent showed a descending curve He found also that a flat curve was produced by persons between the ages of o and 40 an ascending curve by those between 40 and 70 and a flat or descending curve by those showing evidences of arteriosclerosis Green and coworkers[9] in newer experiments produced fat tolerance curves by feeding lipoidol

The diagnostic value of fat tolerance curves produced by alimentary hyperlipemia is limited and can not compare with that of a sugar tolerance curve because the conditions of sugar absorption and combustion are not affected by as many factors as are those of fat metabolism

Wendt and Hirsch also reported a lack of alimentary hyperlipemia in cases of atrophic liver cirrhosis Elmer and Scheps[1] did not agree with these investigators on the diagnostic value of this observation It seems that alimentary hyperlipemia does not appear regularly in diseases where fat absorption is altered It may not be found in such diseases as pancreatic diseases chronic enteritis obstructive jaundice hepatic and atrophic cirrhosis Because the absence of alimentary hyperlipemia depends upon so many factors its diagnostic value is ambiguous and must be considered with reservations The same reservations must be taken for the diagnostic evaluation of alimentary hyperlipemia for example if the duration of alimentary hyperlipemia is longer than seven hours in obese patients

Stanley and Thannhauser[33] recently approached the problem of the etiology of hyperlipemia i e the appearance and disappearance of fat in the serum after the ingestion of fat by feeding of olive oil tagged with radioactive I^{131} to normals and to cases of hyperlipemia The I^{131} in the serum samples was determined with the Geiger counter The amount of radioactive fat given was very small to , grams containing for each meal 100 micro Curies The curves obtained in the serum of normals are in respect to the time of the peak , to 6 hours and in respect to the disappearance of the radioactive I^{131} (about 4 hours) similar to the tolerance experiments with 100 gm of olive oil In cases of essential hyperlipemia and in nephrotic hyperlipemia the peak in the serum was reached at the same time as the normal (see Fig a) However the peak was 3 to 4 times as high and the disappearance of iodine was considerably prolonged in comparison to normal These tracer curves with I^{131} show that the height of the peak and the time of disappearance of fat are mainly influenced by the amount of neutral fat present in fasting

examination found hemoconias in the blood two to three hours after 50 grams of butter had been given the patient

The fasting values of neutral fat in the serum are reported in the older literature as 400 to 600 mgm per cent These figures are much too high and erroneous The serum does not contain more than 0—200 mgm per cent neutral fat in fasting condition For a fat tolerance test Burger[10, 11] gave an oil breakfast of 100 grams of olive oil with a few drops of peppermint to improve the taste or 100 grams of olive oil with 5 grams of cholesterol dissolved in it Hejda[7] gave a fat meal consisting of 50 grams of butter The subsequent meals did not contain any fat A daily curve of fat values obtained at 1 to 2 hour intervals after the tolerance meal by milrofat determination with a lipokrit[8] method shows an increase of about 100 per cent after 3-7 hours and a return to the initial value after 12 to 24 hours (Fig 2) The highest point of the curve depends on the fasting value It must be determined hourly because the peak, which is not always reached at the same time in

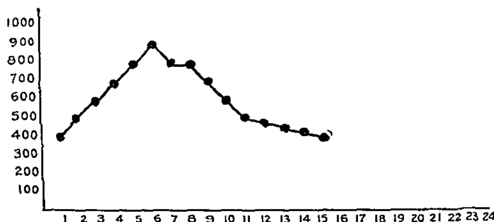


Fig 2 Alimentary hyperlipemia after feeding 100 gm olive oil The first value is the fasting value with the lipokrit method This method gives much too high values (Fasting figures for neutral fat are not higher than 0 200 mgm per cent)

normal persons depends on the individual rates of fat absorption and fat deposition

Burger and his associates[11] reported that there may be an absence of alimentary hyperlipemia after an olive oil breakfast in the following conditions pancreatic diseases biliary obstruction chronic enteritis tubercular peritonitis and amyloidosis Absence of alimentary hyperlipemia is considered of diagnostic value in cases of liver cirrhosis

the most impressive have been the experiments of Wassermann[15] and Hausberger.[1] The nerves for the fat depots are derived from the peripheral nerves.[1] They enter the fat depots with the blood vessels which they follow until they reach the fat cells. The mobilization of fat is controlled by central nervous impulses traveling along the peripheral nerves (Wertheimer[6, 41]). The nervous impulses are thought to influence an enzymatic system in the fat cells themselves. As a result neutral fat is liberated for transportation partly as neutral fat and partly as cholinphosphoric esters, i.e. lecithin. Transport hyperlipemia therefore characteristically consists mainly of neutral fat and to a lesser degree of lecithin and cholesterol. This increase is also pertinent to hyperlipemia due to starvation or anemia. Observations have shown that hyperlipemia after such conditions as bleeding, purpura, leukemia and cachexia also belong to this group.

Studies during the war made on former inmates of Japanese concentration camps showed very low cholesterol values in the serum. Neutral fat was not determined in this extensive study of prisoners of war by P. I. Mitman (personal communication). The question seems to be open whether in these cases neutral fat was increased and cholesterol low or both were low in these food deficient and starved soldiers. Similar studies in Germany on chronically undernourished people also showed low cholesterol values.[42] The level of the neutral fat in the serum during starvation seems to be dependent on whether the examination is carried out at the beginning of starvation, when the fat depots are still present, or after long starvation, when the fat depots are depleted.

It has been suggested that in starvation and after loss of large amounts of blood metabolites originate in the organs from a lack of food or oxygen.[41] These metabolites are conveyed by the blood stream to the controlling nervous organs, where they initiate a mobilization of fat from the depots. This kind of a mechanism was suggested by the classic experiment of Miescher[43] on the Rhine salmon. Yet it must be admitted that despite the neurosurgical experiments on sectioning of the spinal cord in the midthoracic region (Wertheimer[6]) or the cutting of the peripheral nerve where it enters the fat tissues (Wassermann[26]), the neurochemical mechanism of fat mobilization and consequently the mechanism of transport hyperlipemia is not entirely clear.

The type of hyperlipemia and hypercholesteremia observed in "true lipoid nephrosis," as well as in the nephrotic stage of chronic glomerulonephritis, probably also belong to the transport hyperlipemia group. The different possibilities leading to this hyperlipemia will be discussed

condition in the serum The more fat present in the serum before feeding small quantities of radioactive I^{131} containing olive oil the slower is the disappearance of the I^{131} containing fat It seems that the time of disappearance as well as the height of the peak is a result of the amount of the neutral fat already present before feeding

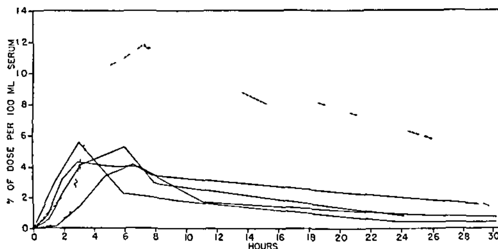


Fig a Curves obtained after feeding 2 to 5 grams of radioactive olive oil each meal containing 100 micro Curies of I^{131} The *straight* lines are curves obtained in 4 normal persons ages 0 to 63 The broken lines are curves obtained with the same amount of I^{131} containing olive oil in 2 cases of idiopathic hyperlipemia

The assumption that fatty substances are absorbed more rapidly and efficiently in cases of persistent alimentary hyperlipemia is not tenable Persistent alimentary hyperlipemia more likely may be the result of a sluggish deposition of fatty substances from the capillaries into the organs of fat metabolism and storage

2 Hyperlipemia Due to Overabundant Mobilization of Fat from Depots Transport Hyperlipemia

The fat depots in the subcutaneous tissue and in the mesentery are under nervous control They are also under hormonal influence Of the many investigations which have demonstrated the nervous control

the most impressive have been the experiments of Wassermann[56] and Hausberger[1]. The nerves for the fat depots are derived from the peripheral nerves[4]. They enter the fat depots with the blood vessels which they follow until they reach the fat cells. The mobilization of fat is controlled by central nervous impulses traveling along the peripheral nerves (Wertheimer[60, 61]). The nervous impulses are thought to influence an enzymatic system in the fat cells themselves. As a result neutral fat is liberated for transportation partly as neutral fat and partly as cholinphosphoric esters, i.e. lecithin. Transport hyperlipemia therefore characteristically consists mainly of neutral fat and to a lesser degree of lecithin and cholesterol. This increase is also pertinent to hyperlipemia due to starvation or anemia. Observations have shown that hyperlipemia after such conditions as bleeding, purpura, leukemia and cachexia also belong to this group.

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The type of hyperlipemia and hypercholesteremia observed in true lipoid nephrosis, as well as in the nephrotic stage of chronic glomerulonephritis, probably also belong to the transport hyperlipemia group. The different possibilities leading to this hyperlipemia will be discussed

extensively in the section on hyperlipemia due to 'lipoid nephrosis" (see section on later page headed Hyperlipemia in Lipid Nephrosis ')

The mechanism, which in these instances initiates the influx of fat and cholesterol from the depots to the blood seems only partly related to the decrease of proteins in the serum Hyperlipemia occurs in animal experiments where there is a depletion of proteins from the serum It is believed that the lowering of the colloid osmotic pressure by a decrease in serum proteins plays an important part in the release of the fat transport mechanism[1] Even if there is no proof for this hypothesis the fact remains that hyperlipemia occurs in cases where experimentally or clinically low serum proteins are observed This type of hyperlipemia should be considered as also belonging to the group of transport hyperlipemia

Transport Hyperlipemia in Faulty Carbohydrate Metabolism—The most obvious instances of transport hyperlipemia are conditions in which a disturbance of intermediary disintegration of carbohydrates and fat in the organs is the cause of the fat mobilization from the fat depots

It has been known for a long time that hyperlipemia appears in severe untreated cases of diabetes mellitus[73] However the early conception that the accumulation of fats in the serum of patients with diabetes mellitus was a symptom of acidosis is erroneous, because hyperlipemia may occur in diabetes even though acidosis is not present

The accumulation of fat in the diabetic liver definitely is coincidental with and probably the result of a decrease in the disintegration of sugar in this organ The less sugar is available for combustion, the more fat migrates to the liver where it accumulates and simultaneously produces hyperlipemia The reduced capacity of the liver to disintegrate sugar in diabetes mellitus is corrected by insulin At the same time following the use of insulin the fat disappears from the fatty diabetic liver which becomes normal in appearance The hyperlipemia consequently disappears

Severe hyperlipemia and fatty liver are observed also in a rare disease where the liver is clogged with glycogen which apparently is not metabolized This glycogen storage disease is known as von Gierke s disease In diabetes mellitus the fatty liver and hyperlipemia occur simultaneously with hyperglycemia In von Gierke s disease fatty liver and hyperlipemia occur simultaneously with hypoglycemia There is a different explanation for the lack of utilizable sugar in the liver in von Gierke s disease This absence may be caused either by an increased tendency to form glycogen or to a decreased ability to transform glycogen into utilizable

sugar. The cause of the disappearance of utilizable sugar in the liver and serum is entirely different in von Gierke's disease and diabetes mellitus but the effect on the fat metabolism is the same in both diseases, that is, the occurrence of fatty livers and hyperlipemia. It is obvious that fatty livers and hyperlipemia result in both diseases from a decrease of carbohydrate disintegration in the liver. In diabetes mellitus the faulty carbohydrate disintegration is restored by insulin and the fat therefore disappears from the liver and blood. In glycogen storage disease, on the other hand, insulin would act in the opposite direction. Up to now hyperlipemia and fatty livers have not been influenced in von Gierke's disease by any kind of treatment.

In experimental diabetes fatty liver and hyperlipemia are observed in depancreatized dogs shortly after the removal of the pancreas. These diabetic animals can be kept alive for a long period by the injection of insulin. A fatty liver and hyperlipemia are found at necropsy. If in addition to the insulin the animals are fed whole pancreas, hyperlipemia and fatty liver are prevented. Dragstedt prepared an alcoholic extract of the pancreas which prevented the accumulation of fat in the livers of depancreatized animals. He believes that the pancreas not only acts on the carbohydrate metabolism of the liver by means of insulin but that it influences also the fat metabolism with another substance produced by the ductless glands of the pancreas. He named this substance "lipocaic" factor.

Best and his coworkers demonstrated that the occurrence of fatty liver in depancreatized animals and in rats on excessively high fat diets could be prevented by feeding these animals choline or lipids such as lecithin, which contains choline in its molecule. Rather large amounts of *choline are required to prevent the accumulation of fat and hyperlipemia.* Best believes that the effect of the "lipocaic" factor of Dragstedt is identical with its choline content. This opinion, however, does not coincide with the fact that the pancreas extracts prepared according to Dragstedt contain only traces of free choline.*

Fatty liver and hyperlipemia may be cured in severe cases of human diabetes by insulin alone. Depancreatized animals with hyperlipemia, however, require in addition to the insulin whole pancreas or large

* Schmidt, Hecht, Strickler and Thannhauser [b] demonstrated by a new method of determining glycerol phosphorylcholine that Dragstedt's lipocaic extract as well as fresh pancreas contains sizable amounts of this substance. It is apparent that the presence of bound choline, i.e. glycerylphosphorylcholine in Dragstedt's extract would explain its lipotropic activity.

amounts of choline These findings indicate that the etiology of the mechanism of hyperlipemia in severe diabetes and in hyperlipemia in depancreatized animals as well as in patients with recurrent pancreatitis is not the same Hyperlipemia due to diabetes mellitus, functional deficiency of the islets of Langerhans is cured by insulin alone Hyperlipemia and glycosuria appearing after injury of the pancreas, removal of the pancreas or chronic pancreatitis are not affected by insulin In these cases however insulin cures the glycosuria if it is present Feeding of pancreatic extract lipocaic factor of Dragstedt or raw pancreas probably influences the fat metabolism of the liver as well as the resulting hyperlipemia by its content of glycerylphosphorylcholine

A similar combination of hyperlipemia and fatty liver may be the underlying factor in acute and alcoholic intoxication Severe damage of the pancreas has been observed in such cases A chronic state of pancreatitis which may result from the acute stage may lead to hyperlipemia and fatty liver with cirrhosis The experiments of Connor[11] demonstrated that a fatty liver due to alcoholism may be followed by liver cirrhosis It is possible that the toxic effect of the alcohol on the pancreas is a factor in the various circumstances causing the fatty livers in chronic alcoholism It seems however, more likely that anorexia and consequent undernutrition lead similarly as in starvation to fat mobilization transport hyperlipemia and fat deposition in the liver The fat content of the liver in chronic alcoholics disappears after a diet rich in carbohydrates and proteins

Many impressive experiments demonstrate a so called lipotropic effect of choline and choline containing substances as well as methionine and inositol on experimental fatty livers produced in rats by diets deficient in choline and proteins but rich in neutral fat The curative effect of these lipotropic substances in these experiments is attributed to their part in the transmethylation process occurring in the liver which is apparently intimately connected with choline formation (trimethylethanolamine) It is however not proven whether choline or the substances necessary for its formation have any curative effect on fatty livers of heterogenous etiology in human beings The results in rats do not necessarily conform with bedside experience A balanced diet however containing proteins rich in methionine (milk) together with intramuscular injections of water soluble vitamin preparations like solu B (Upjohn) facilitates processes of metabolism in the liver which require vitamins in abundance The deficiency state in most chronic alcoholics is not only due to malnutrition but may be aggravated also by decreased

absorption of vitamins. Hyperlipemia (increased fat transport to the liver) in undernourished patients with alcoholic cirrhosis disappears as soon as the liver regains an adequate functional capacity.

The hyperlipemia produced in geese as a result of stuffing with carbohydrates usually is considered as persistent hyperlipemia. However, a similar condition after overnutrition with starchy foods is not known to occur in men. In von Gierke's disease the anatomical appearance of the fatty liver is like that of a stuffed goose because of the glycogen and fat storage and excessive hyperlipemia. Yet a von Gierke liver is not the *result of an extrinsic alimentary condition*. *It is produced by an intrinsic* abnormality of glycogen formation (see under heading "Hyperlipemia in Glycogen Storage Diseases").

At this point a condition of hyperlipemia should be mentioned which occurs in birds, especially in domestic fowl, during the egg-laying season and which also can be induced artificially in fowls by the administration of large amounts of natural and synthetic estrogens[1, 2, 3, 48b, 48c]. The eggs contain large amounts of all kinds of lipids, which are synthesized in the organs of fat synthesis of the fowl. During the laying period or *during the application of estrogens the lipids are produced in excess and* transported to the ovaries. Hence, together with the increased formation of lipids in the organs of their synthesis (*liver, fat tissues*), the lipids have to be transported to the organs manufacturing the eggs, i.e., to the ovaries. Thus the increased lipid synthesis in the laying fowl is accompanied by hyperlipemia (transport hyperlipemia). The hyperlipemic serum in laying fowls contains neutral fat, phospholipids and cholesterol proportionately. As soon as the laying period stops or the administration of estrogens is discontinued, the lipid content of the serum returns *to normal*. Estrogens do not produce hyperlipemia in man.

3. Retention Hyperlipemia. Hyperlipemia Due to Defective Removal of Fat from the Blood and to Sluggish Deposition in Fat Depots

The deposition of fat in the fat depots as well as the mobilization of fat from these depots depends upon nervous and hormonal control. It has been pointed out already that the enzymatic processes of fat mobilization and fat deposition have not been entirely clarified. A distinction should be made between the deposition of fat in the subcutaneous and mesenchymatous tissues, the physiological organs of fat deposition and

storage and the accumulation of fat in the parenchymatous organs like the liver and kidney. The accumulation of fat in the parenchymatous organs will not be discussed in this section because this process usually is not due to an abnormal deposition but probably is the result of an abnormal metabolism within the epithelial cells of these organs (fat phanerosis) leading to fatty degeneration of the involved cells occasionally with secondary hyperlipemia. This process does not fall within the limits set for discussion.

The speed of fat deposition in normal subcutaneous depots depends upon such factors as the daily fat intake, the nervous system and the endocrine glands controlling the subcutaneous tissue[11]. Hyperlipemia may result from overnutrition with fat, from a damming back of fat in the blood stream[3, 4, 49]. This condition, which may occur in cases where the diet is faulty, resembles persistent alimentary hyperlipemia. It has been observed in some cases of obesity due to overnutrition. If the hyperlipemia is combined with hypothyroidism the hyperlipemia becomes more evident[36].

Van Slyke and his collaborators as well as Achard[1] demonstrated that the speed of removal of blood fat may vary and that paradoxical hypo- and hyper lipemia may be the result of a faulty function of a mechanism concerned with the elimination and deposition of fat from the blood stream.

Holt and coworkers[9] suggested that hyperlipemia due to defective removal of fat from the blood stream may be the etiology of "idiopathic familial hyperlipemia." These cases (see on later pages under heading "Idiopathic (Familial) Hyperlipemia with Hepatosplenomegaly and Secondary Xanthomatosis") are characterized by an enormous increase of neutral fat in the serum as well as by an enlargement of the liver and spleen. The size of these organs varies with the amount of lipids in the serum. The authors in their convincing report state that the hepatosplenomegaly in "idiopathic hyperlipemia" is not the result of a primary disturbance of fat or carbohydrate metabolism in the liver. They believe that the hepatosplenomegaly is caused by hyperlipemia.

It should be emphasized that in contrast to "idiopathic hyperlipemia", a milky serum is almost never found in essential xanthomatosis because in these cases the increased serum lipids are not neutral fat but cholesterol and cholesterol esters. The serum analysis made on Goodman's case by Thannhauser and Reinstein reported in the section in this chapter entitled "Idiopathic (Familial) Hyperlipemia with Hepatosplenomegaly" as well as the findings of Holden and Thannhauser[4] in

cases of idiopathic hyperlipemia with and without slight glycosuria in adults also reported in the clinical chapter on Idiopathic Hyperlipemia support the theory of Holt and coworkers[8] that idiopathic hyperlipemia is an example of a type of hyperlipemia which is caused by a defective removal of fat from the blood stream

Creamy serum accompanied by eruptive xanthoma and occasionally by slight glycosuria is observed in rare cases but the insignificant diabetes is not the cause of the hyperlipemia While the diabetes is controlled by a low caloric diet with restriction of the carbohydrate intake the hyperlipemia nevertheless persists These cases are rather related to the syndrome of idiopathic hyperlipemia with hepatosplenomegaly and secondary xanthomatosis described by Burger Grutz[11] where a sluggish removal of fat from the bloodstream is probably the primary cause of the disease (see section headed Idiopathic Hyperlipemia in Adults with Secondary Eruptive Xanthoma Occasionally Accompanied by Glycosuria and Hepatosplenomegaly)

4 Neutral Fat Content of the Serum in Diseases Where the Intracellular Lipid Metabolism is Disturbed

Virchow described as fat metamorphosis or fat phanerosis a fatty degeneration of the cells themselves in contrast to the fat infiltration and deposition in the organs In the latter case there is a displacement and finally a replacement of the organ cells by fat while in the former the cell is not displaced but changed in appearance and content

Fat phanerosis in the opinion of the author is a disturbance of the cellular metabolism especially of the intracellular lipid substances

Macleod and Smedley Maclean[391] described a condition of yeast cells where the intracellular metabolism is altered by starvation The yeast cell converts acetate to long fatty acid chains as well as to neutral fat and to cholesterol in a medium which contains only phosphate and acetic acid The accumulation of lipids in the yeast cell under this condition of starvation may reach up to 60% of the cell substance The ratio of neutral fat to cholesterol while these lipids are accumulated within the *starved yeast cells remains constant* It may be suggested that in a condition of cell starvation the formation of citric acid from pyruvate *and oxaloacetate may be diminished Consequently* the citric acid cycle may become insufficient to metabolize the exogenous and endogenous supply of acetic acid to CO and H O Thus acetic acid is used for the

resynthesis of neutral fat and cholesterol (see Krebs Cycle Fig 1 under Disintegration of Fatty Acids in the Intermediary Metabolism) Although a similar intracellular disturbance may occur in cells of mammalian organs and may cause the phenomenon of ' fat phanerosis" there is up to the present no experimental proof of it The incidence of hyperlipemia together with ' fat phanerosis if it occurs at all, is certainly very unusual

Examination of the literature reveals that hyperlipemia (increase of neutral fat in the serum) is believed to be present in the group of diseases designated as lipoidoses that is in xanthomatoses in Gaucher s disease and in Niemann Pick s disease Such an opinion if generalized for the whole group of lipidoses is definitely erroneous Milky serum with its extensive increase in neutral fat is characteristic only of cases of secondary xanthomatosis due to various types of primary hyperlipemia Although a large increase of total cholesterol in the serum is found in the serum of essential xanthomatosis of the hypercholesteremic type (familial hypercholesteremic xanthomatosis) the appearance of the serum in this group is not milky since neutral fat is not or only slightly, increased Slight increase of cholesterol and neutral fat however is found in the terminal stage of Niemann Pick s disease In Gaucher's disease all the lipid components of the serum (cholesterol phospholipids and neutral fat) are low There has been no report so far of a milky serum in this disease

In summary it should be emphasized that hyperlipemia is not a clinical feature in the group of diseases in which the intracellular lipid metabolism is disturbed

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endothelial cells and histiocytes (Aschoff and pupils) It was suggested that only this group of cells mesenchymal phagocytic cells is involved in the diseases characterized by the accumulation of lipids within the cell As a result of this concept on the idea of a strict neoplastic growth had to be abandoned and the disease was placed in the group of systemic diseases However the question still remained as to whether the lipids are brought to the cell by the blood stream and stored in the cell *or whether the lipids are built and retained within the cell*

The reticulo endothelial system is composed of the following cells (1) the reticulum cells of the epithelial organs lymphatic glands and bone marrow ( ) the peri adventitial cells of the liver capillaries lymph sinuses splenic sinuses bone marrow suprarenals and hypophyseal capillaries (3) the phagocytic cells in the connective tissue and the adventitial cells surrounding the blood vessels throughout the body Cells of this type are found also in the circulation where they are present as monocytic elements

The second advance was made with the chemical identification of the substances The chemical content of the large foamy degenerated cells was determined definitely It was found that the cholesterols are mainly accumulated in xanthomatosis (Pick and Pinkus[3]) A second group of diseases Gaucher s disease is characterized by an increase of only the cerebrosides i e Kerasin (Epstein[11-11] and Lieb) and glucosidocerebrosides (Aghion Halliday and coworkers[16]) The large pale cells of a third group Niemann Pick s disease are composed mainly of the diaminophosphatide sphingomyelin (Klenk)

Ludwig *Pick*[34] *suggested that the accumulation in these cells is* etiologically due to an increased supply of the substances by the blood stream to the reticulo-endothelial cells where they are retained He believed that this process is analogous to the phagocytosis of vital dyes which also are retained in the same cells after they are taken up by the blood stream In accordance with this conception the lipidoses were considered to be storage diseases of lipid substances which are not disintegrated in the intermediary metabolism and are stored in the reticulum cells Thannhauser and Magendantz[4] demonstrated that the basis of this hypothetical mechanism namely an increase of the respective lipid substances in the blood stream does not meet with the chemical findings of the serum It was found that cholesterol is increased in only one type of xanthomatosis and normal in another Normal figures were found for cerebrosides in the serum of Gaucher s disease as well as for sphingomyelin in the serum of Niemann Pick s disease Thann

PART III

XANTHOMATOSES

General Introduction

The etiology of the large pale cells which were found first in "vitiligoidea planum et tuberosum" by Addison and his pupils[1], has been a subject of discussion ever since their discovery almost one hundred years ago. The content of these cells was not differentiated in the early histological observations; the first histological observation was by House in 1873. It was not known that cholesterol, cerebrosides and sphingomyelin were distinct chemical entities. Anatomical research was concentrated on the histogenesis and behavior of the cells. Different forms were described. Although the chemical content of these cells was not known, distinct histological differences were observed. However, during the years of early study it was not so much the content of these cells as the mechanism of their formation that was the main point of discussion.

The early investigators considered the cell growth as neoplastic and tumor-like. Virchow[418] spoke of a fibroma lipomatodes. Pye-Smith[343, 344] on the other hand could not decide whether xanthelasma is analogous to chronic inflammation with fatty degeneration as may be found in the intima of the arteries in arteriosclerosis or whether the xanthomatous tissue resembles those forms of sarcoma with fatty degeneration of reticular or endothelial cells.

The conception that the large pale cells are the manifestation of a metabolic disturbance was presented first by Pick and Pinkus[330, 333]. They did not believe that the pathological changes producing the cells were either neoplastic or the result of simple hyperplasia. They suggested that the cell content with its chemical substances, the lipids, infiltrates the cells from the blood stream as a result of a general disturbance of the intermediary lipid metabolism. Diseases like diabetes and alkaptonuria were compared with the disturbance and it was suggested that large pale cells should be produced as a result of a similar general disturbance of the lipid metabolism.

The first important advance in the research of lipidoses was made with the introduction of the conception that not every cell in the organism may become a xanthoma cell. A group of cells was defined according to their functional behavior. These cells were designated as reticulo-

intima of the arteries, i.e. atheroma, and at the other it resembles those forms of sarcoma or connective tissue growths which show a tendency to a fatty infiltration, and here xanthoma would approach in its anatomical character to the fibroma lipomatodes which Virchow describes.' He also maintained that "... we have in this apparently insignificant affection of the skin a pathologic process exhibited which may throw light on the all important relation between inflammation, degeneration, tissue growth and formation of tumors."

Pick and Pinkus[130] (1908), the first investigators to report that cholesterol and cholesterol esters are accumulated in the blood, suggested that an increase of cholesterol in the blood causes a corresponding increase of this substance as well as fat in the cells. This theory is supported by the fact that in essential xanthomatosis cholesterol is found increased in the serum.

At the same time Aschoff and his pupils[6,5] developed a theory favoring that of Pick. They believed that there is a system of cells, reticulo-endothelial system, which takes up and retains fat and substances of high molecular size from the blood stream. Anitschkow[9,10] (1913), also working in Aschoff's laboratory, was the first to recognize the origin of xanthoma cells as reticulo-endothelial cells.

Many investigators attempted to demonstrate the mechanism of the foam cell by feeding cholesterol dissolved in oil to rabbits. The finding of foam cells, especially in the aorta of animals in atheroma formation, seemed to support the theory that xanthoma formation is the result of hypercholesteremia resulting in cholesterol infiltration. Chauffard,[8,9] who even compared the xanthoma cell formation with gout, coined the term "lipoid gout." This name is erroneous because the diseases compared are entirely different in their mechanism. Today, however, it is known that this kind of experimentation does not prove the mechanism of xanthoma cell formation. First, rabbits cannot be compared with carnivorous animals and human beings since rabbits absorb and retain animal cholesterol, which they excrete in only small amounts.[3,3-383] Secondly, hypercholesteremia is found only in one group of cases of essential xanthomatosis.

Bloch[44] and Schaaf[64] attempted to explain the mechanism of xanthoma formation by another theory. They believe that the lipid mixture in the body fluid may be disproportioned on one side by an increase of cholesterol and cholesterol esters, thus giving rise on the other side to the formation of xanthoma.

Thannhauser and Magendantz in their paper[4,7] and the author in the

hauser and Magendantz[4] therefore, suggested that the mechanism causing this group of diseases which are designated as primary lipidoses, essential xanthomatosis Gaucher's disease and Niemann-Pick's disease is an intracellular disturbance of the lipid metabolism

The group of diseases belonging to the primary lipidoses are considered as systemic diseases The substances which are accumulated in the cell in Gaucher's as well as in Niemann Pick's disease are not supplied by the blood stream They are built and retained within the cell

Historical Notes on the Classification of Xanthomatoses

Rayer[330] (1835) described xanthelasma of the eyelids as plaques jaunatres des paupieres Addison and Gull[4] usually are credited only with the description of the same manifestation which they called vitiligoidea planum et tuberosum These authors however, deserve credit for other early observations

In their classical paper On a certain affection of the skin, vitiligoidea—(a) plana (b) tuberosa with remarks[4] they reported three different kinds of xanthomatous skin affections as well as the involvement of the tendons intima of the bile ducts and blood vessels in the disease A detailed description of the eruptive form of xanthoma in a diabetic patient also was included in this paper

Further histological studies were carried on at the Guy's Hospital by Addison's pupils, Murchison[303], Fagge[1] Moxon[300], Frank Smith and Pye Smith[313, 314] In these investigations the systemic character of the disease was recognized It is difficult to understand why this early conception of the disease was not assimilated in the later literature

Pavy[307] (1866) and Waldeyer[410] (1871) found that the cells xanthoma cells contained sometimes so-called fat granules In subsequent studies mainly the etiology of the fat cells was discussed Virchow[418] (1871) did not consider the change as a true metamorphosis In his opinion the nodular lesions were benign neoplasms infiltrated with fat House (1873) on the other hand suggested that the fat cells had the same origin as the pyoid cells in inflammatory tissue He found that 'vitiligoidea takes origin in a kind of chronic inflammation or a kind of chronic cell growth

Pye Smith[314] (1877) who took a middle position between these two opinions made the following assertion that at one end xanthelasma is strictly analogous to a chronic inflammation of the deeper part of the

cholesteremic group is derived from laboratory findings, while lipid granuloma designates the histology of the lesion present in the normocholesteremic group[43, 44]. It had been pointed out by the earlier investigators (Rowland[3, 6-33], Chester[1], Fraser[14]) that nests of foam cells or single cholesterol containing histiocytes are a part of a granulomatous tissue comprising reticulum cells, leucocytes, groups of round eosinophilic cells, fibroblasts and connective tissue. The systemic nature of this special type of xanthomatous disorder was indicated by the *description of the generalized form of this granulomatous disease*, in which all the organs mentioned are found affected. On the other hand the disease may appear in a monosymptomatic form, where only one organ like the skin or bones is involved[118]. Schuller Christian's syndrome is an incomplete manifestation of the generalized form. It was suggested that the foam cells in the granulomatous tissue are derived from cells of reticular or histiocytic origin as a result of an intracellular metabolic disorder of these cells. Some of the histiocytes and reticulum cells possess the possibilities of embryonal fat cells to form and retain all kinds of lipids within the cell. Clinically the normocholesteremic group is entirely distinct from the hypercholesteremic group, since both syndromes manifest themselves in different organs. The skin is the only organ affected in both groups. However, the appearance, as well as the location, of the skin lesions is different in each division. No hereditary tendency is observed in cases of the normocholesteremic disorder (lipid granuloma).

More recently the pathologists Lichtenstein and Jaffee[8] and S. Farber and coworkers[109, 110, 16] on the basis of histological studies designated as "eosinophilic granuloma" the syndrome formerly described as Schuller Christian's disease (Rowland[3, 61]), lipid granulomatosis (J. Fraser[15] and W. Chester[43]) or as essential xanthomatosis of the normocholesteremic type (Thannhauser and Magendantz[2]). There is no question but that all these authors refer to the same systemic granulomatous disease with different designations. Eosinophilic granuloma is synonymous with Schuller Christian's disease, lipid granuloma, essential xanthomatosis of the normocholesteremic type (see further discussion of the classification). The studies of I. F. Holm, G. Teilum and E. Christensen[42] contributed greatly to the understanding of the histopathology of the granulomatous lesions. They distinguished four phases of development: (1) reticulo-histiocytic proliferation, (2) granulomatous phase with increase of blood vessels and fibrils, reticular cells and histiocytes, eosinophiles and giant cells and incipient lipid accumulations, (3) a

first edition of this chapter of Lipidoses distinguished three different clinical syndromes of xanthomatoses according to the different clinical and laboratory findings

The *first group* involves singly or in various combinations the skin with tuberous or plain xanthomatous lesions the tendons the intima of blood vessels and endocardium and in rare instances the large bile ducts It is characterized by an accumulation of cholesterol and cholesterol esters in a transparent clear serum in which lecithin and neutral fat are normal or only slightly elevated The designation "essential xanthomatosis of the hypercholesteremic type' (hypercholesteremic familial xanthomatosis) was suggested for this group The etiology of the accumulation of cholesterols in the serum was seen in an increased synthesis of cholesterol occurring together with an imbalance of the excretory mechanism of cholesterol The familial occurrence of the primary hypercholesteremic group was demonstrated

In the first edition of this discussion the author expressed the opinion that xanthomatous biliary cirrhosis also belongs to the group of "primary essential xanthomatosis of the hypercholesteremic type' This conception had to be corrected on the basis of new pathological findings in liver biopsies and autopsies It became evident that xanthomatous biliary cirrhosis is a clinical entity by itself caused by a primary liver disorder and characterized by fibrotic changes in the finest interlobular bile capillaries The appearance of wide spread skin xanthoma of the tuberous and plain variety in xanthomatous biliary cirrhosis is secondary to an extreme hypercholesteremia and hyperlecithemia It is characteristic of this disease that neutral fat in the serum is normal or even low

The *second group* of xanthomatous disorders in contrast to the hypercholesteremic group showed normal cholesterol as well as normal lecithin and neutral fat values in the serum It was therefore designated as essential xanthomatosis of the normocholesteremic type in 1939 by Thannhauser and Magendantz[47] Chester (1933)[83] and Fraser (1935)[112] demonstrated that the lesion which they had designated is lipid granuloma is histologically a granulomatous lesion which in its later stages shows accumulation of foam cells in the lesion Thannhauser and Magendantz (1939)[47] established on the basis of their clinical laboratory and histological observations as well as from the cases in the earlier literature that the organs involved in the normocholesteremic group in contrast to those affected in the hypercholesteremic group are singly or in various combinations the skin the osseous system the brain the dura the lungs, the pleura the lymph nodes the liver and the spleen The term normo-

The cells which vary in size and form contain abundant cytoplasm and one or two nuclei In contrast to the cells in Gaucher s and Niemann Pick s disease more than two nuclei are not found in the xanthoma cell The cytoplasm in its fresh state is loaded with small droplets of a fatty substance When it is treated with fixing reagents to dissolve the fat the cytoplasm becomes a fine mesh like network (not vacuoles) giving a foamy appearance Therefore these cells which were originally called Schaumzelle in German have been named foam cells

Examination of a fresh specimen by polarized light shows both isotropic and anisotropic fatty substances in the cells and tissues The cells containing cholesterol break down and leave cholesterol crystals in the softened tissue The foam cells may disappear entirely in later stages The nodules then will have the appearance of a fibroma or simple scar tissue The finding of an occasional giant cell may lead to the erroneous conclusion that the lesion is the result of a foreign body

Foam cells stain yellow or red with Sudan III and slightly pink with Nile blue sulphate The double refraction which is visible in polarized light is indicative of cholesterol esters Extracellular deposits in the tissue especially in the eruptions of secondary xanthomatosis are made visible by fat stain

Chester[3, 84] had already pointed out that one could distinguish two histologically different types of xanthomatous lesions one almost without fibroblasts or granulomatous reaction and the other with granulomatous tissue so prevalent that it is called lipid granuloma (synonymous with the lesion in essential xanthomatosis of the normocholesteremic type eosinophilic granuloma eosinophilic xanthomatous granuloma) Histological examination of the xanthomatous skin lesion of essential xanthomatosis of the hypercholesteremic type (xanthoma tuberosum et planum) shows the xanthoma cells in a fibromatous tissue and the prevalence of fibroblastic elements Histiocytic proliferation together with numerous eosinophiles is not found in this type of lesion In contrast to tuberous and plain xanthoma the lesion of xanthoma disseminata of the skin (lipid granuloma eosinophilic granuloma eosinophilic xanthomatous granuloma) is characterized by reticulo histiocytic proliferation in a granulomatous tissue with development of xanthoma cells in a later phase The histology of the three types of skin lesions characteristic of the different groups of xanthomatous diseases is discussed in detail in the sections on Essential Xanthomatosis of the Hypercholesteremic Type Eosinophilic Xanthomatous Granuloma (essential xanthomatosis of the normocholesteremic type eosinophilic

xanthomatous phase with nests and isolated foam cells, (4) a fibrous stage considered a healing phase

In the *third group* of xanthomatous disorders the outstanding feature is the increase of neutral fat in the serum, i e hyperlipemia (milky serum) In these cases a two to three fold increase of cholesterol in the serum occurs together with a five to forty-fold accumulation of neutral fat If there is an eruption of skin xanthoma these lesions disappear as soon as the hyperlipemia is controlled by elimination of neutral fat from the diet The foam cell and xanthoma formation result in these cases from fat and cholesterol infiltration into the macrophages For this reason this group of disorders in which hyperlipemia is the etiological factor in the xanthoma formation was designated as secondary xanthomatosis due to hyperlipemia'

The classification of xanthomatous disorders according to their clinical and laboratory findings as suggested by Thannhauser and Magendantz was helpful in establishing three different clinical entities of xanthomatous diseases

Anatomical Characteristics of Skin Xanthoma

Four different types of xanthomatous skin lesions are found in xanthomatoses, (1) plain and tuberous xanthoma (2) xanthoma disseminatum (3) eruptive form of nodular xanthoma and (4) eruptive papulo-vesicular lesion in xanthomatous biliary cirrhosis Each type of xanthomatous skin lesion is typical of a different group of xanthomatous disease The lesions of tuberous xanthoma are carotene like or orange, those of xanthoma disseminatum are maroon lemon-like or chamois Both essential and secondary xanthoma are characterized histologically by large pale cells which have a foamy appearance after fixation in alcohol

The first accurate description of the xanthoma cells was given by Chambard[3] (1878) Their relation to reticulum cells and histiocytes was not recognized histologically until the time of Pick and Aschoff and his coworkers It was formerly believed that the cells were related to the sebaceous glands They were even considered to be of parasitic origin The idea that they are a special kind of fat-loaded cells of a benign tumor may even be discussed today This theory is closely connected with the definition and interpretation of what should be called new growth

by the reticulum cells and histiocytes causes a pathological change of the tissue forming xanthoma. Although this hypothesis has been accepted widely in the literature, proof is lacking for the prerequisite of this assumption, namely, the existence of such a disease as a general disturbance of the intermediary cholesterol metabolism.

Examining the weak point of this hypothesis, Bloch[44] and Schaaf[363] stated that cholesterol is only one element in a very complex mixture of *fat and lipids in the substance. They give the following explanation:*

This mixture of lipid constituents does not exist in the serum in a dissolved form but in the form of a finely dispersed emulsion. The normal proportion of all lipids must be maintained in the blood. If the proportion is changed in any *direction, i.e., if the proportion of cholesterol* to lecithin or to cerebrosides or sphingomyelins is altered, the result according to the laws of the colloid theory is a disturbance in the stable aqueous lipid emulsion which the serum represents. The particles become coarser, the emulsion separates, and finally there is a precipitation *of one or all of the individual constituents in the blood* and tissues and a deposit of material so that xanthomatosis results.

The hypothesis of Bloch[44] and Schaaf[364, 365] also has as a prerequisite an extra cellular general metabolic disturbance of the lipids. It was suggested that, *as a secondary result,* lipids are deposited in the reticular cells and tissue. However, there is no proof of a colloid decomposition of the serum or cell fluids resulting in precipitation. There is also no evidence that a disproportion of the lipids in the serum or tissues may lead *to a flocculation of the* colloid mixture. *Deposits of lipids,* especially cholesterol, are found in the deteriorated tissue and in places where cells containing cholesterol undergo destruction. Up to the present we do not know of a spontaneous decomposition of a colloidal system of lipids in the serum, even when the constituents of this system are changed markedly in their relation to each other. The colloid systems protected by different mechanisms in the organism cannot be compared with the colloid systems prepared in the test tube. It is only partially and inadequately possible to copy the constituents of the colloid mixture in the body. The hypothesis of Bloch[44] and Schaaf[364, 365], which adds a second theory to the assumption of extra cellular disturbance of the lipid metabolism, has not been proven at all. It also does not stand critical analysis from the chemical point of view or from experience.

This author (Thannhauser[483]) considers three different possibilities for the etiology of cholesterosis in cells and tissues:

1. *Cholesterol infiltration into the cell* is a process which results

granuloma) and Secondary Xanthoma due to Hyperlipemia (see respective sections)

Pathogenesis of Xanthoma Formation

Waldeyer[44] (1871) believed that the cells of xanthoma planum later called foam cells were embryonal fat cells He suggested that these cells had the possibility of forming different kinds of fat which could be released by degeneration Virchow[444] used the term xanthoma multiplex molluscum lipomatoides for xanthoma disseminatum of the skin which he described as small benign neoplasms This theory was generally accepted in the literature Ce sont donc les cellules endotheliales des espaces lymphatiques qui par leur proliferation, forment la tumeur xanthomateuse These were classified as endotheliome' by de Vincentis[44] Poensgen and Koebner[16] however agreed with Waldeyer that the cells which remain in an embryonal stage produce a so called embryonal lipoma by *their proliferation and adipose metamorphosis* Torok[418] stated that xanthoma should not be classified as true tumors He suggested an abnormality of formation, that is 'il (xanthoma) se forme du tissue a une endroit heterotopique et il est constitue en raison meme de cette heterotopie par des cellules adipeuse a evolution interrompue incomplete (embryonale)

Pinkus and Pick[333] (1908) found the fat substances in the xanthoma lesions to be double refractile lipids cholesterol and cholesterol esters They suggested that xanthomatosis may arise from hypercholesteremia According to these authors Cholesterol infiltration of certain cells takes place because of an increased cholesterol supply from the blood This hypothesis was advanced after Aschoff and his pupils had demonstrated that reticulo endothelial cells were able to take up different kinds of dyes as well as fat like substances from the blood Anitschkow[9,10] at Aschoff s Institute found that foam cells could be produced by feeding cholesterol to rabbits He also demonstrated that the same cells which changed to foam cells took up substances foreign to the body such as dyes The reticulo-endothelial system a classification made by Aschoff embraces all those cells which are characterized by the ability to store double refractile substances as well as dyes

Believing that hypercholesteremia is essential for the formation of xanthoma many investigators naturally assume that the surplus of cholesterol is due to a general disturbance of the intermediary cholesterol metabolism They suggest that this surplus which is taken up and stored

is the primary cause Parallel with the degree of hyperlipemia inflammatory skin xanthoma appear and disappear In visceral organs only few scattered foam cells may be found

The concentration of cholesterol in the serum seems to depend upon many factors Some of the possible causes are discussed as follows

1 *Hypercholesteremia and Xanthoma Formation*

Hypercholesteremia and xanthoma formation may result from

a *Diminished destruction of cholesterol* —Thus far no enzyme capable of splitting the terpen like ring system has been isolated from mammalian tissues The chemical changes which occur in the intermediary metabolism of the cholesterol molecule take place in the side chain of that molecule, such as esterification of the alcoholic hydroxyl group hydrogenation and oxydation of the sterol ring as well as of the side chain It is not definitely known whether the sterol sex hormones are metabolites of cholesterol or the result of sterol synthesis notwithstanding the fact that pregnandiol glycuronate *containing deuterium* was isolated from the urine of a pregnant woman after feeding of cholesterol[1] containing deuterium Cholesterol derivatives in minimal quantities have been isolated from animal organs It was suggested that cholestenone was present in deposits of cholesterol in the arterial wall[316, 27] *Hydrocholesterol has been isolated from the liver and from the serum of pregnant mares*[3] Dicholesteryl ether is present in the spinal cord of the ox[401] Cholestenone is produced by the action of proactinomyces upon cholesterol[28]

A destruction of the cholesterol skeleton was concluded from negative cholesterol balance experiments[330, 186, 87, 317, 90, 51] In these balance experiments cholesterol was determined as cholesterol digitonid From *the fact that the expected amount of cholesterol did not precipitate with* digitonin it cannot be concluded that the cholesterol skeleton was destroyed in the intermediary metabolism The sterol nucleus may well be intact while oxidative or reductive changes may have resulted in a sterol unprecipitable with digitonin or not giving the Liebermann Burchard test Since it has been shown that *bacteria present in the intestinal* tract transform cholesterol to a sterol not precipitable by digitonin[4, 11] it may be concluded that the deficit of cholesterol in balance experiments in animals, as well as in man is due to a bacterial action upon cholesterol in the intestines rather than to a disintegration of the sterol

from an accumulation of cholesterol and cholesterol esters in the serum (hypercholesteremia)

2 *Cholesterol accumulation and retention within the cell* may originate from an increased synthesis and retention of cholesterol in the cell itself This process is effected without increased supply of cholesterol and cholesterol esters from the blood stream

3 *Extracellular precipitation or crystallization of cholesterol,* as it may be observed within the inflamed wall of the gallbladder or the degenerating wall of an arteriosclerotic vessel, may occur without an increase of cholesterol in the serum It is due to degenerative changes of the surrounding medium altering the physico-chemical state of the substances which are not in ionized solution in bile or serum like cholesterol and part of the calcium

The first and second mechanism may result in xanthoma cell (foam cell) formation characteristic of the different types of xanthomatoses

Thannhauser and Magendantz[17] and Thannhauser in the first edition of this discussion classified the xanthomatous disorders according to the laboratory findings in the serum of these patients The figures resulting from the quantitative analysis of lipids in serum are characteristic of three different groups of xanthomatous diseases and hence of great value for their differential diagnosis

1 High serum cholesterol, normal cholesterol cholesterolester ratio moderately increased lecithin in serum but normal or slightly increased values of neutral fat (serum is transparent) are found in essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial xanthomatosis) Characteristic of this group are tuberous or plain xanthoma of the skin (yellow-carotin like in color), xanthoma of the tendon atheroma formation of the intima of blood vessels and of the endocardial lining of the heart, xanthoma of the lining of the bile ducts

2 Normal cholesterol normal lecithin normal neutral fat values of the serum are found in eosinophilic xanthomatous granuloma (normocholesteremic xanthomatosis synonymous with eosinophilic granuloma Schuller Christian s syndrome) The organs involved in this syndrome singly or in various combinations or generalized, are the skin ("disseminata type of skin xanthoma) osseous system, dura brain lungs pleura lymph nodes and spleen

3 Enormously increased values of neutral fat (milky or creamy serum) but only moderately increased values of cholesterols and lecithins are characteristic of idiopathic hyperlipemia with secondary eruptive xanthoma and of related syndromes in which severe hyperlipemia

outside the liver It is suggestive that the clinical syndrome designated by Thannhauser and Magendantz as primary essential xanthomatosis of the hypercholesteremic type (familial hypercholesteremic xanthomatosis) with hypercholesteremia but normal lecithin and neutral fat content of the serum as the leading clinical signs—is the result of increased cholesterol formation in the organism possibly in the liver The exact site of the increased formation of cholesterol however, has not yet been ascertained

This syndrome (hypercholesteremic familial xanthomatosis) is characterized by (1) xanthoma formation of the skin (xanthoma tuberosum et planum) (2) xanthoma of the tendons (3) xanthoma of the intima (atheroma) of the blood vessels and of the endocardial lining of the heart The incidence of this syndrome in families as a hereditary stigma is of great interest The complete syndrome may be present in members *of the same family while in others only familial hypercholesteremia may* be found (incomplete form forme fruste)[3 1 10 4]

c *Increased formation in liver and impaired excretion*—An imbalance of cholesterol formation and excretion is suggested as the cause of xanthomatous biliary cirrhosis The clinical syndrome of xanthomatous biliary cirrhosis is characterized by the following clinical symptoms[4 9 191 41 134 1] (1) skin xanthoma of the plain and tuberous variety (2) enlarged liver and spleen (3) obstructive type of jaundice of years duration (4) extremely high values for total cholesterol (increased 4 6 times those of normal) and very high values for lecithin (increased 4 8 times those of normal) (5) transparent serum and diminished values for neutral fat in the serum despite the outstanding increase of cholesterol and lecithin

On the basis of newer anatomical observations this author has reconsidered his previous opinions concerning xanthomatous biliary cirrhosis[11] and now suggests that the imbalance of cholesterol and lecithin formation and excretion is at the outset a functional disturbance of the liver[40] In later phases inflammatory changes around the bile capillaries (cholangioles) lead to a special type of biliary cirrhosis MacMahon and Thannhauser[68] in a study of the livers of three patients showing the typical clinical signs of xanthomatous biliary cirrhosis as described in a later paragraph found in the early stages a nonspecific chronic inflammatory reaction centered around the smallest bile ducts and junction ducts of all portal areas There was blocking of the ducts and subsequent intralobular bile stasis The larger bile ducts were patent and free (pericholangiolitic biliary cirrhosis)

ring in the intermediary metabolism *On the basis of our present knowledge an accumulation of cholesterol in the blood serum or in the tissues cannot be explained by a diminished destruction of the sterol ring in the intermediary metabolism*

b *Increased formation of cholesterol*—As stated enzymes capable of splitting the sterol skeleton are not known to be active in the intermediary and cellular metabolism of animals Consequently, an accumulation of cholesterol due to an intracellular enzymatic disturbance is not likely to be the result of a decreased cholesterol catabolism but rather of an increased anabolism i e increased synthesis of cholesterol Earlier investigations of cholesterol metabolism have shown that the sterol-ring system is constantly synthesized in the mammalian organism[9, illegible] Schoenheimer feeding materials containing deuterium demonstrated that the small molecules of 2 and 3 carbon atoms, which may be derived from all three food constituents (proteins, carbohydrates and fats) are the basis of cellular sterol synthesis[38] MacLeod and Smedley MacLean had already shown in 1938 that yeast is able to synthesize more than 50 per cent of its cholesterol from acetic acid using acetic acid labelled with deuterium[6] Bloch in 1942, using labelled acetic acid in experiments with rat liver slices also demonstrated that considerable quantities of cholesterol are synthesized from acetic acid in rat liver[16, 4] The question that arises is which organs and cells are capable of cholesterol synthesis Even if there is no definite answer it is probable that every growing cell during maturation is capable of synthesizing cholesterol This function in later life seems to be maintained in rapidly proliferating histiocytes and reticulum cells in certain disorders where the functional possibilities of embryonal cells especially embryonal fat cells to form all kinds of lipids apparently are preserved[119, 435] In the fully developed organism the liver apparently plays a special part not only in the excretion but also in the synthesis of sterols The experiments of Thannhauser Enderlen and Jenke on dogs with bile fistulas demonstrated that the synthesis of the sterol skeleton of bile acids occurs as a biological synthesis in the liver[illegible] In further experiments it was shown that after liver extirpation in dogs the serum cholesterol is not considerably decreased after -4 hours[illegible] Clinically the lowest cholesterol values are observed in the serum of patients with acute yellow atrophy of the liver[133] This observation supports the theory that the liver plays an important role in the formation of cholesterol in the mature organism Different clinical syndromes may develop whether the increase of cholesterol formation takes place in or

deposition of neutral fat (see section on Hyperlipemia) Whenever neutral fat increases in the serum cholesterol accompanies the neutral fat and results in an increase of free cholesterol and cholesterol present as esters In such cases foam cells are caused by an increased uptake of fat and cholesterol from the serum (cholesterol infiltration) and are observed especially in the skin and to a minor degree scattered in the spleen liver and lungs The clinical syndromes in which *xanthoma formation secondary to hyperlipemia* may be encountered are listed as follows (1) Idiopathic hyperlipemia with secondary xanthomatosis In these cases very slight diabetes may or may not be present Hyperlipemia and xanthoma disappear after neutral fat is restricted in the diet Insulin is not effective in the treatment of hyperlipemia in these cases (2) Hyperlipemia with secondary xanthomatosis due to untreated severe diabetes mellitus In these cases insulin treatment alone corrects the diabetic condition as well as the hyperlipemia and the xanthomatous eruption consequently disappears (3) Idiopathic familial hyperlipemia[108, 1, 0, 41] These cases are influenced favorably by a diet very low in fat The hyperlipemia never completely disappears but is reduced considerably (4) Idiopathic hyperlipemia hepatosplenomegaly and secondary xanthomatosis with hepatosplenomegaly of the Buerger Grutz type[6] is probably a variation of the syndrome idiopathic hyperlipemia (5) Hyperlipemia in chronic pancreatitis also may cause secondary xanthoma formation in rare cases[3, 219, 3] (6) Hyperlipemia in glycogen storage disease (von Gierke s disease) Hyperlipemia sometimes is observed in severe cases of this disorder The occurrence of secondary xanthoma in this disorder however is rare[4, 41, 4, 16]

g *Hypothyroidism*—In cases of hypothyroidism the cholesterol content of the serum is elevated The reason for this increase is not known Thyroid medication reduces the cholesterol level of the serum in these patients In rare cases of hypothyroidism with very high serum cholesterol levels foam cells with xanthoma formation may be found in the skin[21] Neutral fat and total phospholipids are not increased or show only a slight rise[3, 4] In hyperthyroidism the total cholesterol level in the serum is low normal or sometime below normal The cholesterol cholesterolester ratio in hypo- and hyper thyroidism is normal

2 *Normocholesteremia and Xanthoma Formation*

a *Xanthoma formation in essential xanthomatosis of the normocholesteremic type synonymous with Schuller Christian s disease*

Xanthomatous biliary cirrhosis' is an independent clinical syndrome In contrast to the author s previous opinion the xanthoma formation of the lining of the bile ducts with resulting obstruction is not considered as the cause of xanthomatous biliary cirrhosis", since it was not found in three autopsied cases[68] For this reason it is believed that xanthoma formation of the lining of the bile ducts may occur in rare cases, similar to atheroma formation in arteries as one of the possible features of the disease but not as the cause of the disease

d *Impaired excretion due to hepatitis* —In almost all cases of epidemic hepatitis or of toxic hepatitis in its acute or chronic stages the total cholesterol in the serum is increased The value of cholesterol present as esters in the serum (normally 70-75 per cent of the total cholesterol) decreases in proportion to the severity of the acute liver cell damage During the patients convalescence the total cholesterol as well as the cholesterol present as esters gradually becomes normal again In chronic hepatitis the values for the total cholesterol are slightly increased while the cholesterol present as esters remains low In acute yellow atrophy of the liver the total cholesterol is below normal signifying that not enough functioning liver parenchyma remains for cholesterol syn thesis In these cases the lowest cholesterol values are observed (Ester Sturz)[431]

e *Mechanical obstruction of the common bile duct* due to stone in flammation or tumor results in a retention of all bile constituents and consequently of cholesterols The serum of patients suffering from mechanical obstruction of bile ducts does not usually show extremely high cholesterol figures (one two times that of normal) The ratio of cholesterol cholesterol present as esters is only altered, if acute or chronic damage of the liver cells accompanies the mechanical obstruc tion[67 68 1 1 1 2 1 431]

Hypercholesteremia of greater degree (3 4 times that of normal) may develop after injury of the common bile duct during an operation resulting in its complete obliteration Notwithstanding complete ob struction of long duration skin xanthoma usually do not develop The occurrence of secondary xanthoma has been reported only very rarely and these have disappeared after the patency of the common duct has been restored[1 3]

f *Hyperlipemia* —The cholesterol content of the blood serum may be increased without functional or mechanical impairment of choles terol excretion in cases where *hyperlipemia* ('creamy serum) occurs Hyperlipemia may be due to an increased transportation or diminished

elements and therefore designated the lesions as xanthomatous lesions, lipid granulomatosis or cholesterol granulomatosis. W. Ceelen (1933)[2] and G. Gerstel (1935)[1,5] suggested that the systemic process is the primary feature of the disease while the foam cells appear in later stages. Lichtenstein and Jaffee (1940)[8] reported cases of solitary bone lesions of this disease. Previously J. Fraser had published cases with solitary bone lesions in a detailed and excellent histological study in 1934-35. The main histological features of these lesions, namely the reticulo-histiocytic proliferation, the increase of eosinophilic cells in the granulomatous tissue and the gradual development of foam cells in the lesion, were shown in colored pictures. He designated such bone lesions as lipoid granuloma. Lichtenstein and Jaffee apparently believed that this type of granuloma was a disease hitherto not described and named it eosinophilic granuloma. It was not until the studies of S. Farber[1, 9, 131, 169] and I. F. Holm, G. Teilum and L. Christensen[3] that the designation of eosinophilic granuloma was applied not only to single bone lesions but also to those of the Schuller-Christian syndrome as well as to the generalized lesions in other organs of the group clinically classified by Thannhauser and Magendantz as essential xanthomatosis of the normocholesteremic type. Through the studies of G. Teilum and coworkers it was demonstrated histologically that the natural history of such an eosinophilic granuloma comprised the following different phases: (1) A proliferative phase in which reticulo-histiocytic proliferation associated with accumulation of eosinophilic leucocytes is observed. In this phase there is no evidence of foam cells. (2) A granulomatous phase with increase of blood vessels and fibrils, reticular cells and histiocytes, eosinophiles, giant cells (Touton cells) and incipient lipoid phagocytosis. (3) A xanthomatous phase with nests of and isolated foam cells. (4) A fibrous stage considered as a healing phase. These four phases often show no strict demarcation during the course of the disease and their histological features may overlap considerably. The paper of Lichtenstein and Jaffee has caused considerable misunderstanding about the classification of the disease under discussion as is obvious from recent publications such as the one of Weinstein and coworkers[4, 4]. It is evident that solitary eosinophilic granuloma is the monosymptomatic early stage of a systemic disease designated by J. Fraser and W. Chester[11, 83] as lipid granulomatosis, by R. S. Rowland[3, 8-361] as Schuller-Christian's disease and by Thannhauser and Magendantz[4, 14, 47] from the clinical point of view as essential xanthomatosis of the normocholesteremic type. These authors all refer to the same

lipid granulomatosis eosinophilic granuloma eosinophilic xanthomatous granuloma—Pinkus and Pick [illegible] were the first to discover that the fat substances in the foam cells are cholesterol and cholesterol esters These authors advanced the theory that cholesterol infiltration of certain cells takes place because of an increased cholesterol supply from the blood In the syndrome under discussion xanthoma cell formation occurs without increased cholesterol supply from the blood, i e with normal cholesterol values in the serum Waldeyer[419] already had suggested that the xanthoma cell is an embryonal cell capable of forming different kinds of lipids which are retained within the cell and only released by disintegration of these cells Since reticulum cells and histiocytes may retain the functional possibilities of embryonal cells it can be assumed that they may be capable also of forming various kinds of lipids including cholesterol It is conceivable that in these cells an inherent metabolic potentiality or a disturbance of the intracellular enzymatic systems concerned with the formation of cholesterol may result in an accumulation of cholesterol within the cells thereby transforming them into xanthoma cells (foam cells) It may be understood that under these abnormal conditions the excess of cholesterol formed is retained within the cell and is not released into the blood stream Such an explanation was applied by Thannhauser and Magendantz[1, 11, 47] to the pathology of a systemic disorder showing histologically xanthomatous and granulomatous features They designated this syndrome as primary essential xanthomatosis of the normocholesteremic type singling out the normal cholesterol content of the serum as the leading sign for the different diagnosis

It was emphasized by these authors that certain organs may be involved singly or in various combinations in this systemic disease The organs which may be affected are the skin (disseminata type of xanthoma) the osseous system dura brain lungs pleura liver spleen and lymph nodes[1, 16, 47] Involvement of the dura brain and osseous system is known as Schuller Christian syndrome[8] Rowland (1928–29)[359–361] W Chester (1930)[83] and J Fraser (1934)[14] in their pioneer work on the histology of the xanthomatous lesion in Schuller Christian syndrome had already demonstrated clearly that this lesion is granulomatous in nature (lipid granulomatosis W Chester J Fraser) The presence of numerous eosinophiles as well as histiocytes and reticulum cells in the granulomatous tissue had already been observed by these authors These early investigators were however more impressed by the nests of foam cells in the granulomatous lesions than by the eosinophiles and histiocytic

the organ itself as a result of increased cholesterol formation within certain cells capable of cholesterol synthesis These cells mostly of reticular and histiocytic origin form and retain cholesterol thus gradually developing the features of foam cells

The following analyses of organs illustrate this interpretation

(a) *Lymph Node* Concentration expressed a percentage of dried tissue Serum cholesterol within normal range (S J Thannhauser and H Reinstein)

		Normal
Total cholesterol	17 9	0 6– . 3
Free cholesterol	-	0 5– 1 1
Cholesterol present as esters	15 7	0 2– 1
Total phospholipids	6 4	5 5–11 0
Sphingomyelin	Traces	0 5– 4 5

(b) *Dura Mater* Concentration expressed as percentage of weight of dried tissue (A H Biggenstoss L F Rosenberg and A L Osterberg)

Total cholesterol	18 58
Free cholesterol	3 2
Cholesterol present as esters	15 3
Lecithin	1 6

(c) Analysis of a *xanthoma dissemınata lesion of the skin* (H Montgomery and A L Osterberg[17]) Serum cholesterol within normal range

		Normal
Total cholesterol of dried tissue	4 55	0 15–0 3
Cholesterol present as esters	3 66	
Free cholesterol	0 89	
Total fatty acids	3 64	

(d) Analysis of the *liver* of a case of generalized essential xanthomatosis of the normocholesteremic type, eosinophilic xanthomatous granuloma (xanthomatous phase) (S J Thannhauser and H Reinstein[49]) Serum cholesterols within normal range

disease. The designation of the disease in question as eosinophilic xanthomatous granuloma would satisfy the clinical as well as the histological observations, even if such a classification does not embrace the proliferative reticulo-histiocytic phase.

The recent histological studies of S. Farber[1,9,130,169] and especially of G. Teilum[01] and coworkers contributed to a better understanding of the histology of the lesion. There is, however, one important point in which the author differs from the interpretation of S. Farber and coworkers.[1,9] Xanthoma cell (foam cell) formation is not considered by Farber as one of the pathognomonic features of the lesion. He implies that the xanthoma cell, if present in the granulomatous tissue, develops by cholesterol infiltration into the cells. Cholesterol should originate from the detritus of focal necrosis and should be locally absorbed and stored by the macrophages. The following objections may be raised against this interpretation:

1. A considerable increase of a normal chemical constituent of a tissue can be the result of an infiltration of this substance into the cells due to an increased supply from the blood stream, or it can be the result of an increased formation of this substance within the cells of the tissue. A shift of a chemical cellular constituent from one cell, which supposedly has undergone dissolution, to another cell macrophagic in character will not cause a measurable increase of the normal constituents of this tissue, presupposing that a sufficiently large specimen of this organ is used for the quantitative chemical analysis. For this reason the quantitative analysis of a tissue specimen will not show a considerable increase of cholesterol originating from the detritus of microscopic areas of focal necrosis, since the increase of cholesterol in one cell is balanced by the loss of cholesterol from another cell which has previously undergone dissolution.

The quantitative chemical analysis of ½ to [illegible] grams of tissue in the xanthomatous phase of eosinophilic xanthomatous granuloma shows an increase of many times (10-[illegible]0 times) the quantity of cholesterol in comparison with a piece of normal organ of similar weight. These high values of cholesterol found in the tissues cannot be considered as originating from cholesterol infiltration from the serum, since the cholesterol level of the serum in this disease is normal and since there is no analogous process known whereby water-insoluble substances normally present in the serum infiltrate and accumulate in the cells. The enormous increase of cholesterol in the analysed specimen of tissues during the xanthomatous phase of eosinophilic xanthomatous granuloma must originate in

stages of the disease It seems that the evidence points at the present time to a formation of cholesterol within the cell rather than cholesterol infiltration for the explanation of the mechanism of xanthoma cell formation in eosinophilic xanthomatous granuloma For clinical considerations however, the normal cholesterol content of the serum in this syndrome is an important feature for the differential diagnosis from other types of xanthomatoses

b *Local Accumulation of Foam Cells in Inflammatory Tissue or Tumor*—A local accumulation of foam cells may be encountered occasionally in inflammatory tissue or in a tumor growth as in osteomyelitis osteitis fibrosa cystica disseminata xanthomatous transformation of the mesentery xanthoma cells in tumors The serum cholesterols in such instances are normal The mechanism of an occasional foam cell development in a local small well defined area is not yet clarified The pathogenesis of occasional foam cell development in inflammatory tissue and in tumors is probably the same as that assumed for the formation of foam cells derived from histiocytes and reticular cells in eosinophilic xanthomatous granuloma

* * *

A summary of these considerations concerning the different mechanisms leading to xanthoma cell formation suggests a different etiology for the three main groups of xanthomatous diseases

I *Essential xanthomatosis of the hypercholesteremic type* (hypercholesteremic familial xanthomatosis) tuberous and plain xanthoma tendon xanthoma vascular xanthoma are characterized by an accumulation of cholesterol and cholesterol esters in the serum This cholesterol accumulation without a marked increase of neutral fat in the serum is the result of an imbalance of cholesterol production and cholesterol excretion Cholesterol apparently is produced in abundance while the cholesterol excretion is insufficient for the increased supply Since the liver is the main organ of cholesterol and lecithin formation and excretion an imbalance in the functioning of this organ may most likely be an etiological factor in xanthomatosis of the hypercholesteremic type How far the local accumulation of foam cells in the skin and tendons play an active part in the accumulation of cholesterol in the serum is not known

II *Hypercholesteremic and hyperlecithemic xanthomatosis secondary to liver disease* (xanthomatous biliary cirrhosis pericholangiolitic biliary cirrhosis) is characterized by an outstanding increase of cholesterols and

		Normal Liver
Total cholesterol of dried tissue	7 ·5	1 1– 2 6
Cholesterol present as esters	4 55	1 5– 2 1
Free cholesterol	· 70	0 45– 0 55
Total phospholipids	7 40	9 0–11 0
Total fatty acids	9 05	8 6–13 0
Neutral fat	0 71	1 4– 4 0

2 Xanthoma disseminata of the skin the lesion characteristic of this group of xanthomatous granuloma (essential xanthomatosis of the normocholesteremic type eosinophilic granuloma), neither undergoes visible necrosis nor are extensive foci of necrosis demonstrable microscopically which could explain the extensive development of foam cells in the lesion [3, 38]

3 Granulomatous lesions of the skin like those in Hodgkin's disease or mycosis fungoides or infectious granuloma show large areas of necrotizing processes even with macroscopically visible ulceration but no foam cell formation It would not be understandable why foam cells should arise only from the detritus of cells in eosinophilic xanthomatous granuloma while they do not originate from the detritus of other granulomatous lesions where large areas of necrosis are present It is therefore unlikely that xanthomatous cell formation in the xanthomatous phase of so called eosinophilic granuloma is an accidental occurrence originating from the debris of local necrosis The author rather suggests that during the abundant proliferation of reticulum cells and histiocytes in the earlier phases of the disease cells arise which have preserved the inherent ability of the embryonal reticulum fat cell to synthesize and retain cholesterol within the cell, thus developing in a later phase into xanthoma cells (foam cells)[410]

S Farber[1, 9] states that he is not willing to accept the classification of Schuller Christian syndrome in the group of lipid metabolic disorders The author can only agree with this consideration in so far as this syndrome is not caused by a general disturbance of the *intermediary* cholesterol metabolism For the consideration discussed above one may assume that in the course of granuloma formation in the disease under discussion cells mainly of reticular and histiocytic origin intrinsically accumulate cholesterol as a result of an inherent metabolic potentiality or an intracellular metabolic disorder These cells which gradually develop the features of foam cells are as pathognomonic for the disease in the later phases as the accumulation of eosinophilic cells in the early

cellular metabolic process rather than from a cholesterol infiltration supplied by the circulating blood or tissue fluid

According to these considerations the following classification of xanthomatous disorders will be used

I HYPERCHOLESTEREMIC XANTHOMATOSES

A ESSENTIAL XANTHOMATOSIS OF THE HYPERCHOLESTEREMIC TYPE (HYPERCHOLESTEREMIC FAMILIAL XANTHOMATOSIS)

1 Xanthelasma of the eyelids and xanthoma tuberosum et planum
2 Tendon xanthoma
3 Xanthoma tuberosum et planum and tendon xanthoma
4 Xanthoma of the blood vessels and endocardium
5 Familial hypercholesteremia Forme fruste of essential xanthomatosis of the hypercholesteremic type

B HYPERCHOLESTEREMIC XANTHOMATOSIS SECONDARY TO LIVER DISEASE

1 Xanthomatous biliary cirrhosis Pericholangiolitic biliary cirrhosis with tuberous and plain skin xanthoma
2 Rare cases of chronic liver disease with secondary xanthomatoses
 (a) Hemochromatosis hypercholesteremia and skin xanthoma
 (b) Postoperative obstruction of the common bile duct hypercholesteremia and skin xanthoma

C HYPERCHOLESTEREMIA IN HYPOTHYROIDISM

II HYPERLIPEMIA (ACCUMULATION OF NEUTRAL FAT IN SERUM) WITH SECONDARY ERUPTIVE XANTHOMA

A IDIOPATHIC HYPERLIPEMIA WITH SECONDARY ERUPTIVE XANTHOMA

1 Idiopathic (familial) hyperlipemia in children with hepatosplenomegaly and secondary xanthoma
2 Idiopathic hyperlipemia in adults with secondary eruptive xanthoma occasionally accompanied by glycosuria and hepatosplenomegaly

B SYMPTOMATIC HYPERLIPEMIA WITH SECONDARY ERUPTIVE XANTHOMA

1 Hyperlipemia in severe untreated diabetes with secondary eruptive xanthoma

Hyperlipemia in chronic pancreatitis and eruptive xanthoma

lecithin in the serum The values for neutral fat are normal or low in the transparent serum The skin xanthoma are of the tuberous and plain variety and occur together with the obstructive type of jaundice of years duration Foam cell formation in the liver parenchyma itself is not observed It is suggested that the hypercholesteremia and hyper lecithemia result from an imbalance of cholesterol and lecithin formation in the liver together with retention of these substances due to oblitera tion of the finest cholangioles Fibrotic obliteration of the finest bile cap illaries are the only anatomical changes demonstrable in biopsies in the early stages of the disease In the last phase of the disease portal cirrhosis with portal congestion is found at autopsy Xanthomatous biliary cirrhosis is a primary liver disease with secondary development of tuberous and plain xanthoma

III *Secondary xanthomatosis due to hyperlipemia* is the result of fat and cholesterol infiltration into the cell from the circulating blood In these instances the serum is creamy due to an enormous increase of neutral fat in contrast to xanthomatosis of the hypercholesteremic type and xanthomatous biliary cirrhosis where the serum is transparent with an accumulation of only cholesterol and lecithin Creamy serum due to different causes—disturbances in the mechanism of transportation and deposition of neutral fat—always is accompanied by hypercholesteremia and may result in secondary xanthoma formation Jaundice is never present in the various disorders of hyperlipemia and secondary xantho matosis even if the liver and spleen may be found enlarged

IV *Eosinophilic xanthomatous granuloma (essential xanthomatosis of the normocholesteremic type, lipid granulomatosis, eosinophilic granu loma)* is a systemic granuloma characterized by reticulo-histiocytic pro liferation by the accumulation of eosinophiles and by xanthoma cell formation The xanthoma cell formation in this reticulo histiocytic granuloma occurs in later phases of the granulomatous disease Reticulum cells and histiocytes if they have preserved the functional possibilities of embryonal fat cells may synthesize fat and cholesterol and retain them within the cell thereby gradually developing into a xanthoma cell The formation of xanthoma cells in eosinophilic xanthomatous granuloma is regarded by the author as an intracellular metabolic process The normal cholesterol content of the serum which led to the original clinical designation of this group as essential xanthomatosis of the normocholes-teremic type is in conformity with the opinion that the xanthoma cells found in eosinophilic xanthomatous granuloma originate from an intra

C. SUPPLEMENT
1. Lipoid proteinosis
2. Necrobiosis lipoidica diabeticorum

I. HYPERCHOLESTEREMIC XANTHOMATOSES

A. ESSENTIAL XANTHOMATOSIS OF THE HYPERCHOLESTEREMIC TYPE. HYPERCHOLESTEREMIC FAMILIAL XANTHOMATOSIS

Essential xanthomatoses of the hypercholesteremic type include (1) xanthoma tuberosum et planum (2) xanthoma of the tendons (3) xanthomatosis of the endocardium and blood vessels (atheroma) (4) xanthomatosis of the larger bile ducts (5) forme fruste of essential xanthomatosis of the hypercholesteremic type *(familial hypercholesteremia)*

HEREDITY

The familial occurrence of the hypercholesteremic type of essential xanthomatosis is characteristic of this disorder. Essential xanthomatosis of the normocholesteremic type (eosinophilic xanthomatous granuloma) on the other hand never runs in families. Obviously not all clinical features are always present in various members of the same family. Xanthelasma of the eyelids or tuberous xanthoma may alternate with tendon xanthoma (see family trees in this section). Xanthoma of the blood vessels (atheroma) with high serum cholesterol may occur monosymptomatically or may be associated with xanthelasma of the eyelids or with tuberous xanthoma (see family tree of C. Muller in this section). In some members of a family high serum cholesterol values may be the only signs of a so-called forme fruste of the hypercholesteremic type of essential xanthomatosis.

Stecher and Hersh[1093, 1093b] elaborate on the clinical observation of familial hypercholesteremia which is the "forme fruste" of hypercholesteremic familial xanthomatosis described by Thannhauser and Magendantz[illegible] Muller[37] and later by others[illegible]. Stecher and Hersh designate familial hypercholesteremia as "genetic" hypercholesteremia but this author prefers the term familial hypercholesteremia since the genes do not transmit hypercholesteremia as such but probably transmit an enzymatic disturbance which leads in these hereditary cases to hypercho-

3 Hyperlipemia in glycogen storage disease (von Gierke's disease) and eruptive xanthoma
4 Hyperlipemia in lipid nephrosis

III NORMOCHOLESTEREMIC XANTHOMATOSES

A EOSINOPHILIC XANTHOMATOUS GRANULOMA SYNONYMOUS WITH SCHULLER CHRISTIAN SYNDROME, ESSENTIAL XANTHOMATOSIS OF THE NORMOCHOLESTEREMIC TYPE, LIPID GRANULOMA, EOSINOPHILIC GRANULOMA

1 Skin manifestations of eosinophilic xanthomatous granuloma (Schuller Christian syndrome essential xanthomatosis of the normocholesteremic type, lipid granuloma)
   (a) Xanthoma disseminatum of the skin
   (b) Petechiae like lesions of the skin in eosinophilic xanthomatous granuloma (Schuller-Christian syndrome)
2 Diabetes insipidus and xanthoma disseminatum of the skin
3 Eosinophilic xanthomatous granuloma of the bone (eosinophilic granuloma of bone osseous xanthoma)
4 Schuller-Christian syndrome osseous lesions of eosinophilic xanthomatous granuloma (defects in the membranous bones of the skull exophthalmos and diabetes insipidus)
5 Generalized form of eosinophilic xanthomatous granuloma (generalized lipid granulomatosis generalized xanthomatosis of the normocholesteremic type generalized form of Schuller-Christian syndrome acute reticulendotheliosis)

B XANTHOMA CELLS IN INFLAMMATORY TISSUE AND IN TRUE TUMORS

1 Xanthoma cells in inflammatory tissue
   (a) Inflamed tissue showing xanthoma cells
   (b) Inflammatory xanthoma of the breast
   (c) Xanthoma cells in osteitis fibrosa cystica disseminata (fibrous dysplasia)
   (d) Xanthomatous transformation of the mesentery and intestinal lipodystrophy of Whipple
   (e) Xantholipomas
2 Xanthoma cells in tumors
   (a) Nevo-xantho endothelioma
   (b) Xanthomatous polycystic lymphangiomas
   (c) Single xanthomatous giant cell tumors
   (d) Epithelial tumors with xanthoma cells

in tuberous or plain xanthoma of the skin and in tendon xanthoma The designation of juvenile xanthoma does not seem warranted since xanthoma of this group may occur at all ages

Distribution and Race

There is no regional distribution in the different parts of the world The occurrence of xanthomatosis of the hypercholesteremic type is described mostly in white people Although no statistics are available the incidence of cases seems larger in the semitic than in other races

Chemical Analytical Methods

For the determination of *cholesterol* and *cholesterol esters* in the serum various methods are applied by different authors It may be emphasized that a comparison of values of cholesterol and cholesterol esters is only possible if the same method is applied by all authors The method of Schonheimer and Sperry[23] is the most reliable one The normal serum values in adults range between 150 60 mgm per cent for total cholesterol and between 30 60 mgm per cent for free cholesterol The cholesterolesters normally constitute between 70–75 per cent of the total cholesterol in the serum

For the quantitative partition of *phospholipids* in the serum the simple method of Schmidt Benotti Hershman and Thannhauser[30] should be applied For other methods see Part I

The *neutral fat* in the serum is estimated by the determination of the total fatty acids according to Stoddard and Drury[41] With this method the total fatty acids derived from neutral fat and cholesterolester and monoaminophosphatides are estimated For the evaluation of neutral fat the value found for total lipid fatty acids has to be computed according to the formula of Thannhauser and Reinstein[19]

Gm per hundred grams neutral fat = gm per hundred grams lipid fatty acids — (gm per hundred grams cholesterol ester × 0 7- gm per hundred grams total phospholipid × 0 69) × 1 04

The fatty acids derived from cholesterolester and phospholipids are subtracted from the total lipid fatty acids to evaluate the fatty acids derived from neutral fat

The serum of the hypercholesteremic type of essential xanthomatosis is not creamy It is mostly translucent in some cases slightly opalescent

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Etiology

The mechanism of xanthoma formation in general and in the hyper cholesteremic type of essential xanthomatosis in particular has been discussed in the previous section It may be reiterated that in the hypercholesteremic group the xanthoma formation is considered the result of an imbalance of cholesterol production and cholesterol excretion While cholesterol is produced in abundance its excretion does not keep pace with the increased supply Whether the local accumulation of xanthoma cells in the skin and tendons plays an active part in the intracellular production of cholesterol or whether these cells originate by increased cholesterol infiltration as a result of an increased supply from the serum is a matter of speculation

Histology

The histology of the various xanthoma of the hypercholesteremic type is described in a subsequent section It should be emphasized that the histology of xanthoma of the hypercholesteremic type differs from that of the normocholesteremic type (eosinophilic xanthomatous granulomas) In the hypercholesteremic group the xanthoma cells (foam cells) are already found in the first stage of the lesion in a vascular, fibrotic tissue consisting of fibroblasts a few lymphocytes polynuclear cells, endothelial cells and histiocytes in the normocholesteremic group (eosinophilic xanthomatous granuloma) the reticular histiocytic proliferation with accumulation of eosinophiles is prevalent in the first phases and the development of xanthoma cells occurs in a later stage of the systemic granulomatous lesion In the hypercholesteremic type of xanthoma a peculiar kind of giant cell is found the so called Touton cell characterized by several nuclei which surround an opaque cytoplasm in almost a complete circle Sclerosing fibrous tissue after a while may replace the xanthoma lesion The lesion may become soft in some parts and cholesterol crystals appear in the softened material or in the tissue spaces together with extracellular lipids

Incidence Sex and Age

Familial xanthomatosis of the hypercholesteremic type is not so rare a disease as is generally believed There is no preponderance of one sex

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Gm per hundred grams neutral fat = gm per hundred grams lipid fatty acids — (gm per hundred grams cholesterol ester $\times$ 0.72 gm per hundred grams total phospholipid $\times$ 0.69) $\times$ 1.04

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(Fig 3) They are yellowish orange plaques one to thirty millimeters in size and level with the skin or slightly elevated Their consistency is soft and velvety Brownish circles often are found around the eye These manifestations were first called vitiligoidea planum et tuberosum by Addison and Gull[4]

The xanthelasma grow slowly usually appearing when the patient is in his thirties sometimes even in his twenties He often states that his mother or father had the same kind of warts around the eyes These usually remain the only evidence of xanthoma during the entire lifetime of the patient The disturbance in most cases does not necessarily indicate a systemic disease and the involvement of other organs High normal or elevated cholesterol is found with xanthelasma of the eyelids

It is important to differentiate between xanthoma planum of the eyelids and the pinhead sized disseminated xanthoma of the eyelids The first which belong to the xanthoma planum et tuberosum group may occur simultaneously with xanthoma tuberosum of the elbows extensor surfaces and tendons The second which belong to the group of xanthoma disseminatum (see later in chapter under the heading Essential Xanthomatosis of the Normocholesteremic Type Eosinophilic Xanthomatous Granuloma) may occur simultaneously with xanthoma disseminata found on the neck axillæ and in the bends of the elbows and knees In these latter cases the cholesterol in the serum always is normal

Electric or caustic treatment usually has proved ineffective in eliminating the plaques of xanthoma planum These efforts usually are followed by the recurrences of the plaques Xanthoma reappear in the scars even after this treatment Diet treatment for xanthelasma also has been of little avail Although the xanthelasma are in most instances the only xanthoma present in the body *it is worthwhile for the physician to examine* carefully each patient with these signs for involvement of other organs

b Xanthoma Tuberosum et Planum

Since their first description by Addison and Gull[4] (1851) xanthoma tuberosum et planum has been confused with xanthoma disseminatum and the eruptive form of nodular xanthoma in diabetes It was only in the last decade (Polano[337] Montgomery[93-5] Thannhauser and Magendantz[4 7]) that differentiation has been made between the different types of tuberous xanthoma (see later section of this chapter) Xanthoma

However it is never creamy in appearance, if taken in the morning before breakfast A creamy serum always results from a considerable increase of neutral fat In the hypercholesteremic type of essential xanthomatosis the neutral fat, if it is at all increased is only moderately so The term hyperlipemic serum therefore, should be used only in instances where neutral fat is so markedly elevated that it is visible to the naked eye If there is an increase of other lipids, like cholesterol and lecithin the designation hypercholesteremia or hyperlecithemia but not hyperlipemia should be used

The characteristic finding in the serum of this syndrome is an increase of total cholesterol and slight increase of lecithin, the latter expressed in high values for total phospholipids The relation of cholesterol to cholesterolesters is normal, i e the cholesterolesters are present in amounts of 70 75 per cent of the total cholesterol Occasionally the cholesterol ester part is even high It should be emphasized that an increase of neutral fat, if increased at all is not a feature of this type of disease The color of the serum is yellow, probably due to its increased carotin content



Fig 3 Xanthelasma on both eyelids (case VII Mrs J K) Compare with xanthoma disseminatum of the eyelids

1 Xanthelasma of the Eyelids and Xanthoma Tuberosum et Planum

a *Xanthelasma of the Eyelids*

Plain xanthoma (xanthelasma) appear commonly on the eyelids, on the corners of the eye and on parts around the eye subject to pressure

also found in the blood serum Quantitative determination of the carotene was not carried out at the time The blood serum was not milky



Fig 4 Tuberous xanthoma on both elbows (case I Dr O)

Blood sugar (fasting) 86 mgm /

Sugar tolerance curve 7/7/36 Fasting 86 mgm / ½ hour 154 mgm / 1 hour 10 mgm hours 78 mgm / 3 hours 53 mgm / 4 hours 93 mgm / This rather flat tolerance curve does not suggest a latent diabetes

Serum	Van den Bergh	0 54	(direct negative)
	Total cholesterol	476 mgm	
	Free cholesterol	1 5	
	Cholesterol esters	351	(73 ′ of total)
	Total phospholipids	437	(normal 150 to 250 mgm /)
	Neutral fat	456	(normal 0 to 00 mgm /)

Case II E H a forty one year old white single male The patient had always been healthy Examinations of his urine occasionally revealed a slight amount of albumin and a few casts When the patient was about thirty years old small yellow flat elevations began to appear on his skin over the region of both elbows As they did not cause any trouble they were disregarded However most of them were removed by cautery Examination of the blood cholesterol showed 5 0 mgm per cent in the serum On a low fat low caloric diet the lesions did not increase in extent

tuberosum et planum may occur together with xanthelasma of the eye lids However both kinds of skin xanthoma frequently are found as separate clinical symptoms

Histology

The nodules consist of fibrotic tissue interspersed with foam (xanthoma) cells The xanthoma cells are mostly confined to the corium around the papillae, abutting directly on the basement membrane They may extend into the subpapillary region around the blood vessels The earlier stages show close to small blood vessels an inflammatory reaction with an infiltration of some polymorphonuclears, leucocytes lymphocytes and histiocytes While eosinophilic cells may be found in small numbers they do not prevail In a short time the xanthoma cells predominate The protoplasm of the endothelial cells of the walls of the smaller capillaries may also become foamy The xanthoma cell is generally considered to be of endothelial or histiocytic origin So called Touton giant cells are numerous and characterized by the arrangement of their nuclei in a complete circle around an opaque cytoplasm Fibrosis takes place in the involuting lesions In the fibrotic phase the lipid substance may be extracellular Areas of cholesterol clefts and cholesterol crystals are seen in the late phase of the sclerosing lesion

Clinical Cases

Case I Dr O a thirty year old physician suffered from chorioretinitis of the disseminated type Both eyes were affected and he had difficulty with his vision for three years Despite search a definite etiology could not be found Small lesions appeared simultaneously on the elbows knees and buttocks these were diagnosed as xanthoma tuberosum (Fig 4) The patient s main complaint was that he had suffered from fatigue for the previous three years He had no fever or loss of weight His appetite was good He was able to carry on his profession satisfactorily Two children were living and well Physical examination revealed no vascular disease Blood pressure 110/90 Urine findings negative

Yellow pea sized tuberous xanthoma were found on both elbows (Fig 4) There was a marked hyperkeratosis on top of the lesion Similar lesions were found on the knees and buttocks No other xanthoma were observed Mucous membranes were free The palms of both hands were of a yellow or carotene like color The same color which is due to carotenemia was

appeared A fairly large nodule also developed over one knuckle on the left hand The blood cholesterol was 540 mgm per cent The patient stated that he felt quite well although he tired easily He later developed some pain over the right index finger on pressure and also over the left small finger He believed that his shins were unduly sensitive He was treated with lipocaic 5 gm (gr 75) daily and 60 mgm (gr 1) of thyroid per day This treatment however was not successful



Fi 6 Tuberous xanthoma (high magnification) case II E H) Histological slide through the courtesy of Dr Rudolf O good

One brother at the age of forty three was living and well his blood cholesterol varied between 220 and 40 mgm per cent Two paternal uncles and one paternal aunt died of diabetes

Physical examination revealed yellowish discrete elevated nodules over his entire back on the scapula lateral aspect of the abdomen buttocks and extensor surfaces of both arms A large soft yellow nodule was found also in only one of the metacarpophalangeal joints It was not attached to the tendon but was only located in the skin

At the age of thirty eight the patient began to develop substernal constricting pain when he walked fast and when he was exposed to a cold draft of air At that time it did not radiate

One cold day he was unable to start his automobile He gradually developed the same type of anginal pain only this time it persisted all morning and disappeared after he took nitroglycerine The following day he was sent to the hospital where frequent sedimentation rates leucocyte counts and electrocardiograms were done Although the electrocardiograms were

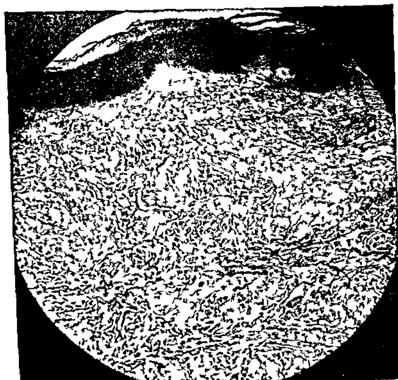


Fig 5 Tuberous xanthoma (low magnification) Note layers of xanthoma cells and granulomatous tissue (case II E H) Histological slide through the courtesy of Dr Rudolf Osgood

not conclusive the increased sedimentation rates the leucocyte counts and elevated temperature bore out the diagnosis of coronary thrombosis While in the hospital the patient had one attack of anginal pain lasting for about ten minutes He stated that there was no drop in blood pressure during his stay in the hospital

At the hospital the patient was placed on a diet of 250 to 500 grams of carbohydrates 80 protein and 40 of fat No attempt was made to eliminate animal foods In spite of this dietary change the lesions on the elbow re-

The plain form of xanthoma or vitiligoidea has the same orange or carotene like color as xanthoma tuberosum The plaques which vary from a few millimeters to five or more centimeters in diameter, are localized on the elbows front of the knees and occasionally the back The center of the lesions may have a yellowish-white discoloration The carotene like pigmentation is increased at the borders of the lesions Nodules may form on the border of the xanthoma Some plain xanthomatous lesions may appear also in an aggregation of tuberous xanthoma Plain xanthoma occasionally are found in the creases of the palms Tuberous xanthoma in rare instances may have the shape of a fleshy, soft tumor beneath the skin without a change of color of the overlying skin (Fig 7) This variety of tuberous xanthoma which bulge the normal skin and give the impression of a subcutaneous tumor are not connected with a tendon but are mostly located under the skin of the fingers toes and buttocks Their histology is not different from that described for tuberous xanthoma



Fig 7 Xanthoma Tuberosum Subcutaneous fleshy nodules of xanthomatous nature verlying skin normally colored

Serum Chemistry —High total cholesterol values (300 800 mgm per cent) are found in the serum The ratio of free cholesterol to ester cholesterol is normal Total fatty acids and phospholipids are slightly increased The increase of total phospholipids is due only to the increase of lecithin Cephalin and sphingomyelin values are normal The slight rise of neutral fats if elevated at all is not high enough to make the serum milky or creamy A translucent or slightly opaque serum may be observed The appearance of the serum is helpful in the differentia

Laboratory Data The fasting blood sugar was 106 mgm per cent The blood sedimentation rate was 7 at the end of one hour by the Westergren method The basal metabolic rate was minus ten A biopsy was made of one of the tendons from the region of the left elbow Examination revealed large nests of xanthoma cells in fibromatous tissue with several giant cells According to the histological and chemical findings this picture was typical of tuberous xanthoma of essential hypercholesteremic xanthomatosis

Chemical Findings	*Found*		*Normal*	
Total cholesterol	364	mgm %	150–260	mgm %
Free cholesterol	100	"	30–35	"
Cholesterol esters	64	7[illegible] % of total	70–75%	of total
Total phospholipids	470	mgm %	150–250	mgm %
Sphingomyelin	17 6		15–30	"
Cephalin	48	"	0–20	"
Lecithin	404 4		150–230	"
Total fatty acids	828	"	190–420	
Neutral fat	3 0	"	0–200	"
Carotene	0 130	"	0 02–0 10	"
Bile acids	negative			

This patient was seen repeatedly during the following years The laboratory findings did not change markedly He died of acute coronary occlusion at the age of 45

Clinical Features

Tuberous xanthoma are nodular elevations on the skin These nodules are not confluent but usually are isolated or aggregated in small groups (Fig 4) Their shape is irregular and their size varies from that of a pinhead to a chestnut The surface has a yellow-orange or carrot-like color Hyperkeratosis may be present on top of the lesion

The lesions usually are located on the extensor surfaces of the arm, elbow and buttocks They may be scattered also on the back and on both sides of the legs but are never found in the axilla or bend of the knees and elbows This localization is important for the differential diagnosis of tuberous xanthoma and xanthoma disseminatum Tuberous xanthoma are not found in the mucous membranes The xanthoma occurring on these places belong to the eruptive form of xanthoma, which is due to hyperlipemia or to xanthoma disseminatum

TABLE III

	% of wet weight	% of dry weight	Normal of dry weight
Total cholesterol	5.5	13.2	0.15-0.3
Cholesterol esters	2.5		
Total phospholipids (called lecithin)	2.0	12.5	
Fatty acids	3.17		

Differential Diagnosis

Xanthoma tuberosum can be distinguished from xanthoma disseminatum and secondary xanthoma of the eruptive nodular type because of differences in (1) location (2) color and (3) group arrangement

Tuberous xanthoma are found on extensor surfaces, elbows buttocks the back and extensor sides of both legs They also appear in the folds of the skin and in areas subject to friction Xanthoma disseminatum is observed on the face around the neck in the axilla (not the outer surfaces) in the bends of the elbows and knees and scattered all over the body The eruptive form of nodule xanthoma is located on the extensor sides of the arms and legs the buttocks and both sides of the waistline In contrast to xanthoma planum et tuberosum these lesions appear and disappear They may involve the mucous membranes mouth lips eyelids and ears They may be scattered also all over the body The eruptive form or nodular form of secondary xanthoma always is due to hyperlipemia A milky serum is not found in patients with tuberous xanthoma

Tuberous xanthoma are orange or carotene in color and exhibit hyperkeratosis on top of the lesion Xanthoma disseminatum is of a maroon chamois or lemon color It sometimes has a shiny appearance Secondary xanthoma of the eruptive nodular type are yellowish brown nodules the tiny heads of which are depressed in the center The latter lesions are surrounded by a small inflammatory halo

Tuberous xanthoma may appear isolated scattered or in small groups of several lesions Xanthoma disseminatum may be found also as scattered or isolated lesions It is often grouped in ridges or clusters from which a single lesion is not easily separated The single lesion may however be pedunculated or "molluscum" Secondary nodular xanthoma are always isolated lesions without any special grouping

tion of tuberous xanthoma from secondary nodular xanthoma, which are found together with a milky serum

The partition of lipids before and after a cholesterol-free diet was determined in the following case of a patient with tendon nodes and xanthelasma of the eyelids (Table II)

TABLE II

	Before Cholestrol free Diet		After Cholesterol – free Diet		
	1/9/39	6/21/39	7/28/39	10/3/39	3/12/40
Total cholesterol	351.0 mgm %	315.0 mgm %	444.0 mgm %	[illegible]4[illegible].0 mgm %	34.0 mgm %
Free cholesterol	109.0 "	85.8	95	87.6	68.6
Ester cholesterol	42.0	9 2	348.8 "	59.4 "	265.4
Total phospholipids	396.0	83.0	364.0	98.0	47.0 "
Lecithin			203.5	02.5 "	
Sphingomyelin			55.5	7.5 "	
Total fatty acids	429.0 "	458.0 "	465.0 "	410.0 "	90.0 "
Neutral fat					None
Carotene	0.620	0.500	0.250 "	0.08 "	0.147 "
Bile Acids					None
Total protein					7.83 mgm %
Albumin					5.02
Globulin					81 "

Analysis of Skin—In the literature the figures for cholesterol and lipids are related to specimens of wet tissue The values of different specimens of wet tissues cannot be compared exactly because of the variation in water content It is also evident from an analysis of a large lesion of plain xanthoma as seen in the following table (Table III), that a comparison of dry weight and wet weight is not adequate

described by Brachet Monnard, Poensgen[33 336] Balzer[9], Richter[3 1] low[9] Arning and Lippmann[14] Ginat[143] Ochs[311] Schmidt[3 1] Schonheimer[4 6], Buerger[1] Raeder[317], Wile[4 3] D E Layani[4] Galloway[146] and

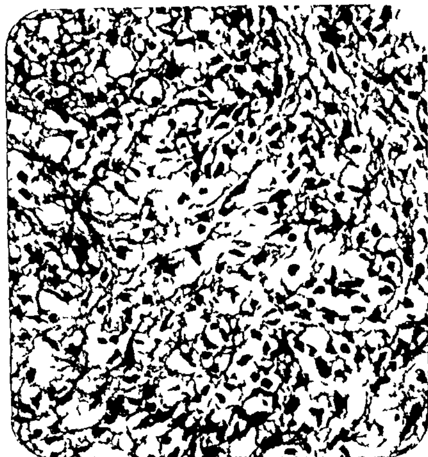


Fig 8 Xanthoma cells in tendon xanthoma Note large amounts of fibrotic tissue (case III R S)

other investigators The fact that xanthoma of the tendons is part of the tendons and cannot mechanically be separated from the tendon was emphasized in the surgical literature by Beelman[3] Brochard Janiel[1] Dean Lewis[31] Romiti[3 1] Ragins[318] Young and Harris[1 3]

A case of a patient with xanthelasma of the eyelids tendon xanthoma

These clinical characteristics may not always be of sufficient help in making a differential diagnosis. The following histological features are noted in skin biopsies of the three different forms of skin xanthoma. (1) Tuberous and plain lesions of essential xanthomatosis of the hypercholesteremic type show numerous xanthoma cells isolated and in nests in a fibromatous sclerosing tissue. These are seen in the corium and around the papillae. Only a few eosinophiles and histiocytic elements are present; fibroblasts and collagenous tissue prevail. (2) In the eruptive form of nodular xanthoma due to hyperlipemia of various etiology only a few scattered foam cells are dispersed within an inflammatory tissue. Considerable amounts of extracellular lipids are visualized with fat stains. (3) Xanthoma disseminatum (normocholesteremic xanthoma, eosinophilic xanthomatous granuloma of the skin) is characterized in the histological section by numerous xanthoma cells beneath the papillae and in the subcutis. Eosinophiles together with numerous histiocytes are the main cellular elements constituting the granulomatous tissue.

Possible Involvement of Other Organs

Tendon xanthoma are found together frequently with tuberous xanthoma. The blood vessels, especially the coronaries, may be involved. The endocardium also in rare instances may be the seat of xanthoma.

2. Tendon Xanthoma

Introduction

Calcott Fox[141] (1879) in England and Carry[71] (1879) in France were the first to describe xanthoma of the tendons. Carry's patient was a member of a family which for three generations had suffered from so-called gout. Although the patient had yellowish xanthoma planum in addition to tendon nodules at the age of seven, the diagnosis of 'gout' had been made previously.

Tendon xanthoma have been called "gout form of xanthoma" even in later publications. This term, however, is misleading. Besnier[39] called this kind of a new growth "xanthoma en tumeur".

Six cases of tendon xanthoma were reported by Startin[409] in 1882. The first good pictures of a patient with tendon xanthoma were published in 1889 by G. Lehzen and K. Knauss[211]. Similar cases have been

of the endocardial linings and valves were present in almost all patients manifesting the clinical syndrome These observations are definitely contrary to L N Foster s conception that the xanthoma cells in tendon xanthoma are an accidental, degenerative phenomenon that is seen in numerous other neoplastic and inflammatory diseases For the explana tion of the pathogenesis of a systemic disorder histological studies applied as the only tool of investigation have their limits especially if only one



FIG 9 Xanth matous nodes of the tendons over the knuckles of both third fingers N te smaller nodes on tendons of all fingers (case III R S)

of the involved organs is examined Xanthoma cells certainly gradually develop in this as in other conditions from endothelial cells and from reticulum cells but their significance for the pathogenesis of the actual disease cannot be decided by the microscope alone (see section on his tory and pathogenesis of xanthoma formation)

Clinical Cases

Case III R S a sixty five year old Jewish widow At the age of thirty five she first noticed burning lumps on the knuckles of the third finger

double cataract of the eye and xanthomatous involvement of the cerebellum and pyramidal tracts was reported by Van Bogaert, Scherer and Epstein[9] This observation on the occurrence of tendon xanthoma with a simultaneous involvement of the nervous system is unique in the reports so far

Histology

The tendon xanthoma are described erroneously as xanthomatous lesions of the tendon sheaths The lesion is however, located in the tendon itself The histology is not much different from that of tuberous xanthoma (see preceding section) Touton cells are less numerous so called foreign body giant cells more frequent The tissue structure of the tendon itself is interwoven with the lesion Sclerosis of the lesion occurs early

L N Foster[110] in a recent histological study of tendon xanthoma which he designates as benign giant cell tumors of tendon sheaths, calls attention to their histological similarity with sclerosing hemangiomas' of the skin described by Gross and Wolbach[1 3] The well-known vascular structure in the early lesion is demonstrated again The more fibrosis and sclerosing tissue develop the less the vascular structure of the early lesion is visualized Fibroblasts and fibrils of collagen become predominant Endothelial cells originating from intravascular cells develop by lipophagic activity into foam cells and xanthoma cells Opinion regarding this process as a metabolic disturbance was not confirmed by this study Although the foam cell has been thought to be the anatomic expression of a disturbed blood lipid stoichiometry fat, appearing in these cells secondarily represents a degenerative phenomenon that is seen in numerous other neoplastic and inflammatory diseases Proliferation of tumor cells occurs before lipophagocytosis is demonstrable and ceases as large amounts of lipids appear in the cytoplasm of the intravascular cell L N Foster thus interprets the xanthoma cell development in tendon xanthoma as a degenerative phenomenon that is seen in numerous other neoplastic and inflammatory diseases This opinion could arise only by his one sided approach to this question in the examination of 42 anatomical specimens of tendons derived from various collections of pathological departments However of 26 of our observed cases of tuberous and plain skin xanthoma as well as those observed by others in many instances atheroma formation of the arteries (angina pectoris, coronary thrombosis) and in rare cases xanthomatous involvement

composed of dense and interlacing cellular strands and bands of collagenous tissue interspersed by innumerable and varying sized groups of large foam cells Occasional binucleated cells and rare mitotic figures were found among the large xanthoma cells



Fig 10 Xanthomatous nodes on both Achilles tendons (case III R S)

A smear from the first specimen showed many cholesterol crystals (Fig 11) Analysis of dry tissue total cholesterol 9 mgm per cent total phospholipids 11 mgm per cent

There was no recognizable change in the size of the lesions of the tendon during the period the patient was on a cholesterol free diet which was not however strictly followed Small xanthelasma like yellow lesions also appeared on the skin of the nose where there had been pressure from her eye glasses

Case IV R S a fifty five year old salesman and brother of the patient described above had for several years noticed nodes on his knuckles He had never been seriously ill and had no complaints A small xanthoma was visible on the extensor tendon of his right fourth finger at the first interphalangeal joint There were also circumscribed swellings 4 × ½ cm on both Achilles tendons The liver and spleen were not palpable At the age of 58 the patient died suddenly of a heart attack A third brother who

of each hand When she was fifty-five similar lumps developed above both heels A small node appeared on the right elbow when the patient was sixty two Circumscribed nodes measuring about 3 × 6 cm and movable only with the movement of the tendon in the region of the phalango metacarpal joint were found in the extensor tendons of both third fingers (Fig 9) There was another small node on the fifth finger of the left hand A large xanthoma node was found in the region of both Achilles tendons (Fig 10) The patient had no xanthelasma The liver and spleen were not palpable Changes in the right knee joint were clinically and roentgenologically characteristic of osteoarthritis No cystic bone lesions were, however present

Table IV gives the cholesterol findings of the blood serum

TABLE IV

Serum	Total Cholesterol	Free Cholesterol	Cholesterol Esters
10/ /35	360 mgm %	00 mgm %	160 mgm %
10/ 9/35	368	-40	1 8
11/ 7/35	347	191	156
11/19/35	351	187	164
11/ 6/35	345	148	197 "
1 / -/35	338	158	180
12/17/35	4 0	-00	220 "
1/15/36	388	198	190
4/17/36	394		
6/ /36	440	1-4	316
7/ 9/36	4 3	163	260
9/10/36	390	70	3 0 "
11/13/36	364	113	-51
/ 0/37	84	100	184

A cholesterol free diet was begun on 10/ 2/35 and continued until the patient was discharged 11/ 9/35 Thyroid extract was administered as follows from 11/-0/35 60 mgm (gr 1) b i d from 11/ 0 to 11/-9/35 1 0 mgm (gr ii) t i d The thyroid was discontinued on 11/-9/35 because of stenocardic complaints

A small subcutaneous nodule appeared below the right knee cap while the patient was being treated by diet The node in the tendon of the third right finger was removed The xanthoma was found to be intimately connected with and situated between the fibers of the tendon The section was

composed of dense and interlacing cellular strands and bands of collagenous tissue interspersed by innumerable and varying sized groups of large foam cells Occasional binucleated cells and rare mitotic figures were found among the large xanthoma cells



Fig 10 Xanthomatous nodes on both Achilles tendons (case III R S)

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did not have tendon xanthoma died also of coronary thrombosis (see Forme Fruste in later section)

Serum total cholesterol	210	mgm %
Serum free cholesterol	107	"
Serum cholesterol esters	103	"



Fig 11 Cholesterol crystals in softened part of a tendon xanthoma (case IV R S)

Clinical Features

Serum Chemistry —Total cholesterol figures are found increased in cases of patients suffering with tendon xanthoma If only tendon xan

thoma without an involvement of other organs is present, the figures may not be very high The figures, 260 300 mgm per cent total cholesterol, are found in cases where only one or two small pin sized xanthoma are detected

The serum is not milky The slight increase of phospholipids in the serum is due to an increase of lecithin but not of cephalin or sphingomyelin If there is a simultaneous involvement of other organs the cholesterol figures are much higher, and the figures for lecithin also increase proportionately

Tissue *Anaylsis*—The following values were obtained from dry tissue (see first case in section headed Tendon Xanthoma) total cholesterol 9 mgm per cent, total phospholipids 11 mgm per cent of the dry tissue

Tendon Nodules—Subcutaneous nodes, arising from fascia ligaments and tendons yet intimately connected with and inseparable from tendons, are found on the Achilles tendon (Fig 10) on the tendons of finger (Fig 9) in the fascia of the periarticular tissue especially on the knuckles extensor ligaments of the fingers phalageal and knee joints and in rare instances on the tendons of the extensor muscles of the legs These colorless nodes which are found under the skin vary from pea sized nodules to egg sized tumors At times there may be additional yellow tuberous xanthoma on the surface of the skin where there is friction or pressure These are found especially on the Achilles tendon or heel The skin over the tumor is movable but the tumor itself is fixed to the tendon

The nodules are firm and hard On rare occasions a small part of the tumor is softened giving the impression of fluctuation In the softened part cholesterol crystals (Fig 11) are present Usually the nodules do not cause pain It is only when they are in close connection with a joint that they may prove troublesome cause arthritic changes in the joint and disturb its function They usually do not exulcerate and drain

Occurring frequently in youth they have been designated erroneously as juvenile xanthoma However they are found at any age and are associated very often with plain and tuberous xanthoma of the skin *and with xanthoma of blood vessels and endocardium* Tendon xanthoma are hereditary and are therefore observed in several members of the same family as well as in various generations of a family

Osteoarthritis and Tendon Xanthoma—Patients with tendon xanthoma not infrequently have arthritic symptoms such as swelling and pain in the joints in the vicinity of the tendon xanthoma Clinically and

L P, a female patient of 48 years under the author's observation has suffered from characteristic attacks of gout for four years (uric acid in serum 6–8 . mgm per cent) A high cholesterol concentration of serum (325–365 mgm per cent) and xanthelasma on both eyelids were found in this patient Blood sugar was normal Two sisters had xanthelasmas on the eyelids Two brothers had high cholesterol values in their serum and had suffered from heart attacks

Xantholipomas within the joint in lipomatous tumors containing xanthoma cells, these are true tumors and do not belong to this group of familial hypercholesteremic xanthomatosis

3 Xanthoma Tuberosum et Planum and Tendon Xanthoma

The combination of yellow xanthoma tuberosum et planum and tendon xanthoma is found mostly in children It is sometimes erroneously called juvenile xanthoma

The interchangeable occurrence of xanthoma planum et tuberosum and tendon xanthoma in a family is best described by the history of one family suffering from the disease (see family tree, Fig 14, appearing in Case VI

Clinical Cases

Case V Marilyn K 13 years (Patient of Dr C G Shapiro Paterson N J) is an only child Her mother has liver cirrhosis Xanthelasma palpebrarum is frequent in the fathers family When the child was nine months the mother observed a pin head sized mass near the babys anal fold Within the next six months tendon xanthoma appeared on the heels gradually increasing in size At two years the girl began to develop tuberous xanthoma on the elbows behind the knees on the buttocks and hands At this time one lesion was removed from the heel followed by the removal of nine more when she was four years of age The patient was kept on a low fat diet for two years but new tumors developed and kept growing bigger Several of these were again removed At ten she had deep x ray therapy for six months over her hands and feet Although these treatments seemed to decrease the growths it was not long afterwards that tumors were again removed from the right and left arm The patient was once more put on a diet without any effect She underwent five operations for the removal of xanthomatous masses The character of the lesions are shown in Figs 12 and 13 The heart sounds of the child were normal



FIG 12 Xanthoma planum et tuberosum on the back side and on the leg and on the buttocks Al o subcutaneous fleshy tumors of xanthomatous nature (Case V Marilyn K case of Dr C. G Shapiro)

Total cholesterol	835 mgm %	
Free cholesterol	28	
Cholesterol ester	607 "	(73% of total)
Bilirubin	0 75 "	

Case VI Mr I K a fifty year old Jewish plumber noticed painless swellings on the knuckles of both hands at the age of thirty years Approximately ten years later swellings appeared on both heels At forty seven he first suffered from attacks of substernal pain which was diagnosed as angina pectoris and responded to treatment with nitroglycerin



Fig 13 Tendon xanthoma on both Achilles tendons and fleshy xanthomatous tumors on both ankles and toes (Case V Marilyn K case of Dr C G Shapiro)

All his four children also showed evidence of xanthomatosis (see family tree) His wife had yellowish brown patches on the eyelids (see Fig 3) One sister of Mrs I K Mrs Ch had xanthoma of the tendons, another sister was supposed to have xanthelasma

Mr I K (Case VI) was moderately obese He was not jaundiced His eyelids showed no xanthelasma Lungs and heart were normal electrocardiogram normal liver and spleen not enlarged

Tendon xanthoma movable with the tendons on the extensor side and most pronounced on the first interphalangeal joint were visible on the third fourth and fifth fingers of both hands Small tendon nodes were

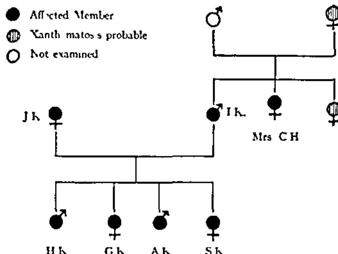


Fig 14 Family tree of family K

present also in the olecranon region Extensive swellings in lower third of both lower legs bulged posteriorly and laterally in the region of the Achilles tendons These nodes were firm and not sensitive Measuring 8 by 3 cm they were larger than those found in any other member of his family

Serum total cholesterol	65 mgm %
Free cholesterol	105
Cholesterol esters	160
Monoaminophosphatide	300
Total fatty acids	496

Case VII Mrs J K forty seven year old Jewish housewife At the age of twenty three shortly after the birth of her first child she noticed brown swellings on both upper eyelids When she was forty these lesions had grown considerably (Fig 3) Similar lesions also appeared on the lower lids Both upper and lower eyelids showed characteristic xanthelasma the smallest measuring 3 mm in diameter the largest 5 by 20 mm They were of soft consistency and elevated 1 to 2 mm above the level of the skin No tumors of any tendons were palpable Liver and spleen were not palpable nor enlarged upon percussion She lost thirty-one pounds in seven months on a reduction diet, but there was no change in her xanthelasma

Total cholesterol	835 mgm %	
Free cholesterol	228 "	
Cholesterol ester	607	(73% of total)
Bilirubin	0 75 "	

Case VI Mr I K a fifty year old Jewish plumber noticed painless swellings on the knuckles of both hands at the age of thirty years Approximately ten years later swellings appeared on both heels At forty seven he first suffered from attacks of substernal pain which was diagnosed as angina pectoris and responded to treatment with nitroglycerin



Fig 13 Tendon xanthoma on both Achilles tendons and fleshy xanthomatous tumors on both ankles and toes (Case X Marilyn K, case of Dr C C Shapiro)

All his four children also showed evidence of xanthomatosis (see family tree) His wife had yellowish brown patches on the eyelids (see Fig 3) One sister of Mrs I K Mrs Ch had xanthoma of the tendons another sister was supposed to have xanthelasma

Mr I K (Case VI) was moderately obese He was not jaundiced His eyelids showed no xanthelasma Lungs and heart were normal electrocardiogram normal liver and spleen not enlarged

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lesions appeared on the knuckles of several fingers There was also an volvement of the skin of the knees and elbows



Fig 16 Xanthoma tuberosum on the buttocks (case VIII G K)

The xanthoma of the skin were round brownish orange flat lesions 3 to 4 cm in diameter with somewhat pronounced margins and sharp borders The center of these lesions was lighter and slightly depressed Similar although smaller tuberous skin lesions were visible in the gluteal folds and flexor aspect of the knees There were in addition tendon xanthoma of the extensor tendons of the third and fourth fingers of both hands and larger xanthoma nodes in both Achilles tendons (Figs 15 18) Liver and spleen were not felt no jaundice

	10/ 0/36	11/-/36
Serum total cholesterol	48 mgm %	533 mgm %
Serum free cholesterol	1 9 "	1 9 "
Serum cholesterol esters	353	404 "
Total phospholipids		394 mgm %
Total fatty acids		585
Neutral fat		9

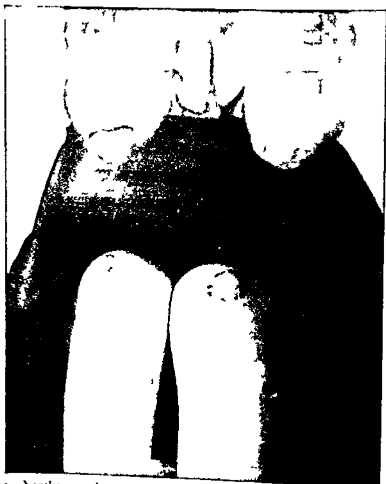


Fig 15 Xanthoma tuberosum et planum on both elbows and both knees The velvet like xanthoma are carotene in color (case VIII G K)

Case VIII Daughter G K an eleven year old intelligent schoolgirl was undernourished and underdeveloped At the age of seven she noticed painless nodes in the regions of both heels One or two years later similar

lesions appeared on the knuckles of several fingers There was also an involvement of the skin of the knees and elbows



Fig 16 Xanthoma tuberosum on the buttocks (case VIII G K)

The xanthoma of the skin were round brownish orange flat lesions 3 to 4 cm in diameter with somewhat pronounced margins and sharp borders The center of these lesions was lighter and slightly depressed Similar although smaller tuberous skin lesions were visible in the gluteal folds and flexor aspect of the knees There were in addition tendon xanthoma of the extensor tendons of the third and fourth fingers of both hands and larger xanthoma nodes in both Achilles tendons (Figs 15 18) Liver and spleen were not felt no jaundice

10/ 6/36	Serum total cholesterol	667 mgm %
	Serum free cholesterol	203 "
	Serum cholesterol esters	464 "
	Total phospholipids	448 "
	Total fatty acids	4 3

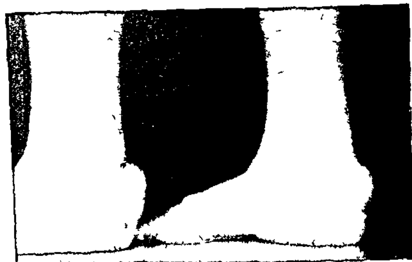


Fig 17 Xanthomatous nodes on both Achilles tendons (case VIII G K)

3/27/37 After moderate restriction of food containing animal fat

	Total cholesterol	785 mgm %
	Free cholesterol	22 "
	Cholesterol esters	563 "

The total phospholipid content of the dried substance of an excised lesion was 1 7 mgm per cent Total cholesterol of the dried substance was 13 1 mgm per cent No sphingomyelin was present When the patient was examined two years later no recurrence of xanthoma was found in the scar

Case IX Daughter S K a twenty-two year old girl had no complaints but had noticed and felt nodes on her heels for two years There was a slight bulging of the region of the Achilles tendons on both sides 5 cm distant from the floor The patient had been obese as a child

Serum total cholesterol	44 mgm %
Serum free cholesterol	83 "
Serum cholesterol esters	161

Son A K a sixteen year old schoolboy had no complaints He showed xanthoma of various extensor tendons of the fingers of both hands and also of both Achilles tendons

Serum total cholesterol	[illegible] mgm %
Serum free cholesterol	97
Serum cholesterol esters	185
Total phospholipids	303
Total fatty acids	354

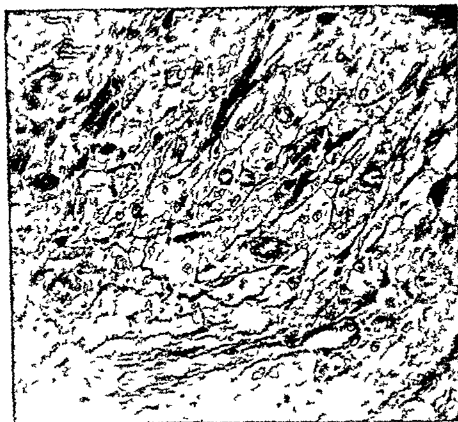


Fig 18 Xanthoma cells in xanthoma planum (case XIII G K)

Case X Son H K a twenty three year old student was in good health and had no complaints There were no pathological findings in lungs or heart blood pressure normal liver and spleen normal Examination of left Achilles tendon revealed a pea sized tendon xanthoma similar to those of his brother and sister Chemical findings in the serum icteric index 13 Van den Bergh less than 0 5 mgm per cent carotene 0 5 mgm per cent (0 02 mgm % normal)

Serum total cholesterol	400 mgm %
Serum free cholesterol	100
Serum cholesterol esters	300 "
Serum total fatty acids	471

Case VI Sister of Mrs K Mrs Ch, a moderately obese housewife fifty-one years old At the age of thirty-seven she had noticed painless lumps on the knuckles of various fingers She showed no icterus There was no xanthelasma of the eyelids Xanthoma were found on three fingers of each hand predominantly in the region of the phalangometacarpal joint Xanthoma - cm in diameter were present also in both Achilles tendons There were small tuberous nodules in the regions of both elbows Liver and spleen were not enlarged

Serum total cholesterol	500 mgm %
Serum free cholesterol	183
Serum cholesterol esters	317
Total phospholipids	63

In the family K both the mother and father had xanthoma The father's family had tendon xanthoma The occurrence of the disease in the mother's family was not ascertained The father had attacks of angina pectoris All children of this couple were found upon examination to have tendon xanthoma One child, G K, had in addition very large xanthoma planum et tuberosum It is remarkable that in the cases of the children who had only small tendon xanthoma the total cholesterol of the serum was not high The highest cholesterol value was found in the case of the youngest child who had xanthoma planum et tuberosum and tendon xanthoma In this case no murmur of the heart was detected a condition usually reported in similar cases in the literature Meanwhile the father I K and two of his sons have died of coronary thrombosis

Cases of similar families with hereditary characteristics have been described by Raeder[4] and Wale and Dumeling[10]

4 Xanthoma of the Blood Vessels and Endocardium

Fagge[1] (1873) mentioned a case with xanthomatous involvement of the auricle, aorta and pulmonary artery Calcott Fox[111], who in 1879 published the first description of the combination of tendon xanthoma with xanthoma planum found a simultaneous involvement of the mitral valve with xanthoma Poensgen[33, 336] (1887) reported the case of an

eight year old boy suffering from tendon xanthoma and xanthoma tuberosum et planum with aortic involvement

Lehzen and Knauss [1] (1889) described an eleven year old girl who like patient G K had xanthoma planum et tuberosum This girl died from an intercurrent infection after an operation The autopsy revealed xanthoma on both the pulmonic and mitral valves and xanthomatous patches in the pulmonary artery The aorta and left carotid showed a xanthoma of the intima simulating a neoplasm which almost occluded the lumen of the vessel Xanthomatous patches the size of a pinhead were found also in both coronaries This patient had a sister suffering from the same disease

Leube who in 1911 discussed the case of this child at a clinical lecture at Wurtzburg called attention to the unusually loud systolic murmurs of the heart and advised examination of the heart in all such cases of xanthomatosis

Similar familial cases with an involvement of the heart and arteries in children have been published by many other authors Arning and Lippman[11] reported one in a family in which the mother and five out of nine daughters exhibited cutaneous lesions Three of these children died suddenly while apparently in good health two others while dancing Death in all these instances was probably due to coronary occlusion Cook Smith Giesen and Berder[40] described a child with xanthoma tuberosum aortic stenosis coronary sclerosis and angina pectoris

Cases of tendon sheath xanthoma with coronary involvement similar to that of family K described by Thannhauser and Magendantz[1] are reported by the Scandinavian authors Harbitz[151] Raeder[31] and Muller[61] and in the preceding section In 26 cases of tuberous xanthoma mentioned by Montgomery[33] one half the patients showed cardiovascular symptoms

Clinical Course and Anatomical Findings

A good description of the occurrence of essential xanthomatosis of the blood vessels and endocardium in youth was given by Hess[19] He presented the case of a nineteen year old girl who always had been in good health She complained of severe dyspnea one evening two hours after supper and collapsed Clinical examination revealed xanthoma of the skin and tendon xanthoma The size of the heart was normal Blood pressure was 100/60 Pulse was very rapid 140 The patient was brought to the hospital in a condition of heart failure and in spite of all

efforts died thirty six hours later A diagnosis of coronary occlusion was made on the basis of xanthomatosis of the skin and tendon xanthoma

The necropsy revealed xanthomatous involvement of the coronaries and diffuse xanthomatous involvement of the endocardium, the aorta and aortic valves (Fig 19) The xanthomas on the aorta as well as the aortic valve gave the impression of little tumors Most of the blood vessels on the trunk, limbs and hands as well as the lung arteries showed yellow patches of atheroma i e xanthoma

Under the microscope the elevated patches revealed more or less intensive hyperplasia of the intima the elastic fibers of which were in



Fig 19 Xanthomatous nodules on and above the aortic valve Reproduced from F O Hess[196]

creased in some places and just visible in others Some extra cellular deposit of fat was also seen The accumulation of foam cells grouped in bands of two or more layers under the endothelium of the vessel, is characteristic of the histological picture (Fig 20)

Short stretches of layers of xanthoma cells are seen piled up over the inner lining of the blood vessel These may extend into or beneath the inner lining of the vessel At the beginning there is hardly any

cellular or fibroblastic reaction In later stages fibrous tissue grows into the lesion and sclerosis prevails Giant cells are not observed in either stage A similar atheromatous lesion occasionally may develop on the inner layer of the large bile duct

Carl Muller[21] described the interchangeable occurrence of tendon xanthoma *erroneously called* xanthoma tuberosum in his study xanthelasma of the eyelids and vascular diseases in eighteen families most of whose family trees were traced The persons affected were mostly

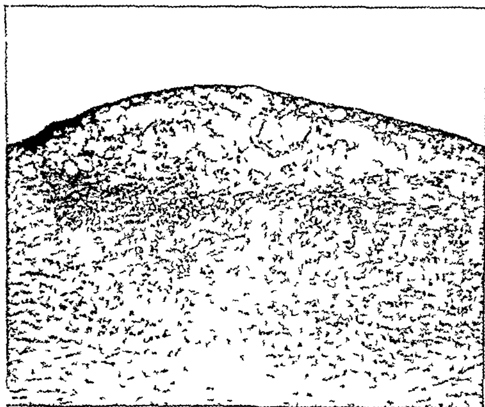


Fig 20 Xanthomatous (atheromatous) nodules of the intima of an artery Histological slide through the courtesy of Dr Timothy Leary

adults between the ages of thirty and seventy This report confirms the author s opinion that juvenile xanthoma is an inappropriate designation for tendon xanthoma This study also shows that vascular diseases especially coronary diseases may occur in familial hypercholesteremic

xanthomatosis in combination with tendon xanthoma or skin xanthoma and as isolated lesions of the blood vessels Mono-symptomatic cases without skin xanthoma but with high serum cholesterol have been described by Thannhauser and Magendantz[1 7], who call them forme fruste of essential hypercholesteremic xanthomatosis (see following section)

Relation of Hypercholesteremic Familial Xanthomatosis to Atheromatosis and Arteriosclerosis (Atherosclerosis)

The occurrence of coronary diseases in essential hypercholesteremic familial xanthomatosis raises the question of the extent to which this type of xanthomatosis is related to atheromatosis and to arteriosclerosis

In the first part of this section the author considered three different possibilities for the etiology of the accumulation of cholesterols in cells and tissues

1 Cholesterol *infiltration into the cell* resulting from an accumulation of cholesterol and cholesterol esters in the serum (hypercholesteremia)

2 Cholesterol *accumulation and retention within the cell* by increased synthesis and retention of cholesterol within the cell

3 Extracellular *precipitation or crystallization* of cholesterol as it may be observed within the degenerative wall of an arterosclerotic vessel or within the inflamed wall of the gall bladder[161] without an increase of cholesterol in the serum It may be due to degenerative changes of the surrounding medium altering the physico chemical state of the substances which are not in ionized solution in the serum like cholesterol and part of calcium

The first and second mechanism may cause xanthoma (foam cell) formation in the arterial wall without any sclerosing processes (atheroma formation) (see Fig o) Occasionally the atheroma may degenerate and sclerosing scar tissue may remain The sclerosing process may involve the other layers of the blood vessels Changes not distinguishable from arteriosclerosis may result

The third mechanism of cholesterol precipitation occurs in sclerotic vessels (arteriosclerosis) secondarily Cholesterol and its esters in the cases of arteriosclerosis are mainly deposited extracellularly[8, 14] Cholesterol esters are visualized by the polarization microscope There may be development of some foam cells secondary to the precipitation of cholesterols in the wall but it is evident that atheroma formation i e

intracellular accumulation of cholesterol is not the common pathway by which cholesterol and its esters appear in the vascular wall of a primary arteriosclerotic vessel

Since atheroma formation on the inner lining of the arteries is found not infrequently with other manifestations of familial hypercholesteremic xanthomatosis the assumption of a common pathogenic principle i e an imbalance of cholesterol production and excretion seems justifiable *Atheroma and tuberous and plain xanthoma are microscopically similar* Singly occurring atheromatous patches in the arterial wall are comparable in their significance for the diagnosis of the hypercholesteremic type of xanthomatosis to isolated neurofibromas for the diagnosis of von Recklinghausen s disease

Unfortunately such atheromatous patches may occur in young individuals not only on the intima of the larger arteries but also on the coronary arteries and may cause occlusion of the coronaries Thannhauser and Magendantz first called attention to the fact that many patients with tuberous and tendon xanthoma die from coronary occlusion *If coronary death occurs in young persons the presence of* atheromatous lesions in the coronaries must always be suspected W Newman[20] recently reported the autopsy of 39 young soldiers who died of coronary disease Atheromatous lesions were found in 37 of these cases Engleberg and Newman[111] also called attention to coronary artery disease in young adults due to hypercholesteremia

The relation between arteriosclerosis and atheroma has been investigated by Leary[14] who demonstrated that xanthoma of the arterial wall *may be produced by feeding rabbits cholesterol It must be emphasized* that the production of atheroma in arterial walls of herbivorous animals like rabbits and chickens[9] [66] by high cholesterol intake cannot be compared with spontaneous atheroma formation in man since herbivorous animals absorb animal cholesterol but cannot excrete it (see section on Cholesterol) Although there is no doubt that sclerotic changes of the vascular wall may be the result of atheromatous patches there seems to be no proof that the development of arteriosclerosis in man begins *primarily with cholesterol deposits in the cells of the vascular walls*[14] [1] [128]

Atheroma formation is always found together with elevated serum cholesterols Crystallization and precipitation in arteriosclerotic blood vessels occur usually without elevation of the serum cholesterols Cases with diffuse xanthomatosis (atheromatosis) of the blood vessels and

endocardium are rare. Scattered areas of atheroma, however, occur frequently. If one of these accidentally is localized in the coronaries, coronary thrombosis may result. These localized xanthoma (atheromas) are referred to as "forme fruste" of familial hypercholesteremic xanthomatosis if no other evidence of xanthoma formation is found elsewhere in the body. Elevated cholesterol in the serum may be the only indication of the existence of a "forme fruste" of xanthomatosis of the hypercholesteremic type (see discussion under Therapy of Essential Xanthomatosis of the Hypercholesteremic Type).

It is commonly assumed[99b, 99, 334] that the accumulation of neutral fat in the serum, i.e., hyperlipemia by itself (as by overfeeding with neutral fats, alimentary hyperlipemia), causes atheromatosis. The author, however, would like to call attention to the clinical observation that in patients with idiopathic hyperlipemia where the increase of neutral fat is 20 to 40 times that of normal and the cholesterol is simultaneously increased to 2 to 4 times that of normal, an increased incidence of atheromatosis such as observed in familial hypercholesteremia has not been reported yet. Neither angina pectoris nor peripheral arteriosclerosis are symptoms of idiopathic hyperlipemia. This is the more remarkable since neutral fat in cases of idiopathic hyperlipemia is permanently increased in the serum. In hyperlipemia secondary to severe untreated diabetes, however, arteriosclerosis is a common occurrence although hyperlipemia in these instances is not permanent. The vascular damage in severe diabetes resulting in arteriosclerosis, therefore, cannot be explained solely by an increase of neutral fat and cholesterol in the plasma.

In summary, it may be stated that atheroma formation and arteriosclerosis in man are not etiologically identical processes. Atheroma formation is primarily connected with hypercholesteremia and is mainly observed as a hereditary constitutional stigma in families together with the trait of familial hypercholesteremia. However, arteriosclerosis (atherosclerosis), in contrast to primary atheromatosis, is a "wear and tear" process of the blood vessels where the fibrillary elastic structure of the vascular wall becomes loose and less elastic. Cholesterol precipitation in the less elastic tissue spaces of the sclerosed loosened wall is a phenomenon secondary to the sclerosis of the wall since degenerative changes of the vascular wall alter the physico chemical stages of such substances in the plasma and tissue interspaces which are not in ionized solution such as cholesterol and part of calcium and result in their precipitation within the vascular wall. The cholesterol in the arteriosclerotic

vessel is mainly deposited extracellularly If, in addition to the extra cellular deposition foam cells are found in the arteriosclerotic wall they originated secondarily to the imbibition of cholesterol by infiltration into the macrophagic cells of the sclerotic vessel It is however evident that atheroma formation i e intercellular accumulation of cholesterol is not the common pathway by which arteriosclerosis originates

5 Familial Hypercholesteremia Forme Fruste of Essential Xanthomatosis

Thannhauser and Magendantz[1 7] described as forme fruste of essential xanthomatosis of the hypercholesteremic type cases in which high serum cholesterol is clinically the only demonstrable sign of this disorder These patients usually complain of tiring easily and of slight stenocardic pains coronary thrombosis occurs not infrequently

Since cholesterol determination of the serum has become a routine procedure in many hospitals the high incidence of high cholesterol values in patients with coronary disease and coronary thrombosis seems more common[19 20] Especially patients of the younger age groups who succumb suddenly to a coronary attack show high serum cholesterols It would be going too far to assume that all younger people with coronary disease belong to this forme fruste group of xanthomatosis This supposition would however be warranted if hypercholesteremia with and without skin and tendon xanthoma is observed in other members of the same family (familial hypercholesteremia)

Clinical Cases

Case XII Mrs F a fifty five year old haggard looking woman was mentally quick and physically very active especially in her household duties Her chief complaint was that for many years she had tired very easily Her skin had a brownish hue like a tan although she had not exposed herself to the sunlight Xanthosis i e a yellowish carotene like color was observed on the soles of the feet and the palms of the hand especially the creases The scleræ were normal No abnormalities of inner organs were discovered There were no signs of hypothyroidism Urine and blood were normal Basal metabolism rate was minus 10 per cent blood sugar 85 mgm per cent bilirubin Van den Bergh 0 5 icteric index 11

endocardium are rare. Scattered areas of atheroma, however, occur frequently. If one of these accidentally is localized in the coronaries, coronary thrombosis may result. These localized xanthoma (atheromas) are referred to as "forme fruste" of familial hypercholesteremic xanthomatosis if no other evidence of xanthoma formation is found elsewhere in the body. Elevated cholesterol in the serum may be the only indication of the existence of a "forme fruste" of xanthomatosis of the hypercholesteremic type (see discussion under Therapy of Essential Xanthomatosis of the Hypercholesteremic Type).

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Differential Diagnosis

Probably doubt exists as to whether there is any justification for designating a "forme fruste" of essential hypercholesteremic xanthomatosis (familial hypercholesteremia). However the cases of Thannhauser and Magendantz[4] as well as those of C Muller[301] provide a basis for distinguishing a "forme fruste" of essential xanthomatosis from hypothyroidism. In the cases designated as "forme fruste" signs of hypothy-

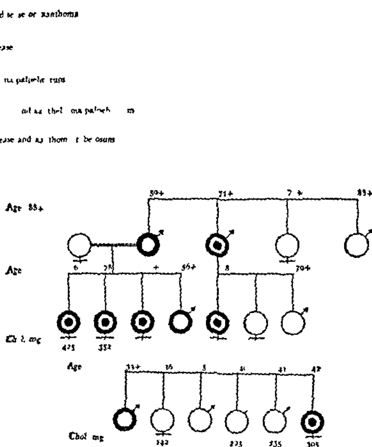


FIG. 21 Family tree of a family reported by C Muller[301]

roidism are absent. The skin is smooth, the hair is fine. The individuals are mentally and physically alert even if they fatigue very easily. The

Total cholesterol	295 mgm %
Free cholesterol	103
Cholesterol esters	192
Two months after cholesterol low diet	
Total cholesterol	76 mgm %
Free cholesterol	75
Cholesterol esters	01
Total phospholipids	290
Total fatty acids	389
Neutral fat	45

Case XIII E de S forty eight year old man several of whose ancestors had diabetes Patient s six children were healthy When he was thirty eight traces of sugar were found in his urine The sugar disappeared without his following a diet At forty two he was examined in Paris Hypercholesteremia without other symptoms was found Four months later after a diet low in fats the total cholesterol was 3 0 mgm per cent The patient followed this diet for six years Cholesterol determination which was repeated several times during 1936 and 1937 showed values of total cholesterol of about 00 mgm per cent Basal metabolic rate was normal on several occasions

The patient was living in the tropics and had to be very active in his business He complained chiefly of physical fatigue His mind on the other hand was quick and agile He stated that at times he had depressed and uneasy feelings as well as occasional symptoms of angina pectoris

There were no signs of hypothyroidism Xanthosis was observed on the trunk and extremities The soles of the feet and the palms of the hands especially the palms had a yellowish carotene like color The size of the heart was normal There was a systolic murmur at the aorta Blood pressure was 135/80 Liver and spleen were not enlarged Blood sugar was 10- mgm per cent, bilirubin (Van den Bergh) 0 5 mgm icteric index 20 This patient recently died of coronary thrombosis

Two years after cholesterol low diet	
Total cholesterol	216 mgm %
Free cholesterol	50
Cholesterol esters	166
Total phospholipids	309

Case XIV T S (age 57) brother of patients (R S and R S cases III and IV in *section headed Tendon Xanthoma*) was in good health He complained for two years of angina like symptoms which occurred during exertion and occasionally in cold weather He died suddenly of coronary thrombosis Muller[2 1] reported a series of similar cases where coronary thrombosis occurred in families with tendon xanthoma (see family tree in Fig 21)

of cholesterol There is no doubt that cholesterol administered in pure substance as it has been done in experiments needs the presence of neutral fat in food in order to be absorbed In food however cholesterol is never present as a pure substance but in an emulsified condition which facilitates its absorption Interpretation of experiments of others led the same authors to conclude that cholesterol is only absorbed if it is present as esterified cholesterol in the chymus of the intestinal contents Pancreatic esterase esterifies cholesterol in test tube experiments In their opinion pancreatic esterase is necessary for esterification of cholesterol for its absorption However, cholesterol esters are already present in the chymus of the intestine since different foods like animal fats and meat contain neutral fat free and esterified cholesterol as well as phospholipids Substantial quantities of esters are therefore already present in the food and do not need to be esterified for their absorption if this is true at all The idea therefore of restricting fat for the sole purpose of preventing esterification of cholesterol should not come into consideration The restriction of fat and meat in the diet however is necessary for another reason namely because of its very content of cholesterol and cholesterol esters

The diet prescribed in essential xanthomatosis of the hypercholesteremic type (familial hypercholesteremic xanthomatosis) should be as low as possible in animal cholesterols but may contain cholesterols derived from plants As pointed out in the physiological introduction animal cholesterol is the only sterol absorbed from the intestines Schonheimer[3 3 3] demonstrated in experiments that plant sterols are not absorbed at all In order to obtain a cholesterol free diet it is therefore necessary to exclude only animal products such as animal fats eggs meat and cream The patient also should be taught that he must cook and prepare the vegetable foods in his diet with fats of vegetable origin like olive oil and pure margarine which have the same nutritive value as animal fats[1 6]

The patient must follow this diet over long periods of time Additional allowances of small quantities of lean meat and lean fish may be given twice a week However the patient should on the whole strictly adhere to the basic diet

The following is an example of a diet low in animal cholesterol

metabolism may be on the lower border of normal but is never as low as in cases of hypothyroidism. In many of these cases the histories show familial occurrence of xanthoma, xanthelasma in the eyelids and tendon xanthoma. However, such an occurrence is not necessary for the diagnosis of "forme fruste."

The differential diagnosis of "forme fruste" from hypothyroidism is of more than theoretical significance. Practically, it is of definite value in the therapeutic treatment of the patient. In the "forme fruste" the patient is helped greatly by the restriction of cholesterol in his diet, in the latter disorder diet restriction is not necessary. Thyroid, in contrast to cases of hypothyroidism, should not be administered to patients with "forme fruste" (familial hypercholesteremia) since thyroid medication leads to angina pains.

THERAPY OF ESSENTIAL XANTHOMATOSIS OF THE HYPERCHOLESTEREMIC TYPE (HEREDITARY HYPERCHOLESTEREMIC XANTHOMATOSES)

Since essential xanthomatosis of the hypercholesteremic type results from the imbalance between the endogenous production of cholesterol and cholesterol excretion, restriction of the exogenous quota of cholesterol, i.e. decreasing the intake of food containing animal cholesterol, can only improve but will never cure the condition. The cholesterol level of the serum in this syndrome will be reduced but will be higher than normal in contrast to the curative effect of diet treatment in hyperlipemia and secondary xanthomatosis.

There is considerable misunderstanding about diet treatment of atheromatosis and arteriosclerosis. Cholesterol free diet in prevention and in treatment of arteriosclerosis will have only a limited effect since marked hypercholesteremia usually is not found in arteriosclerotic individuals. Excluding the exogenous quota of cholesterol in cases of arteriosclerosis does not cope with the pathogenesis of this "wear and tear" disease and does not prevent precipitation of cholesterol in the sclerotic vessels. Only in cases where the cholesterol is high in arteriosclerosis does the restriction of cholesterol containing food seem justified. In atheromatosis, however, due to familial hypercholesteremia, which is a symptom of familial hypercholesteremic xanthomatosis, diet treatment is always indicated, even if the effect of the restriction of exogenous cholesterol does not result in normal values of the serum.

Some clinicians[1,3] would like to restrict only fat as much as possible from the diet in the belief that fat as such is needed for the absorption

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Therapy of Essential Xanthomatosis of the Hypercholesteremic Type (Hereditary Hypercholesteremic Xanthomatoses)

Since essential xanthomatosis of the hypercholesteremic type results from the imbalance between the endogenous production of cholesterol and cholesterol excretion, restriction of the exogenous quota of cholesterol, i.e. decreasing the intake of food containing animal cholesterol can only improve but will never cure the condition. The cholesterol level of the serum in this syndrome will be reduced but will be higher than normal in contrast to the curative effect of diet treatment in hyperlipemia and secondary xanthomatosis.

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B HYPERCHOLESTERLMIC XANTHOMATOSIS SECONDARY TO LIVER DISEASE

1 Xanthomatous Biliary Cirrhosis Pericholangiolitic Biliary Cirrhosis with Tuberous and Plain Skin Xanthoma

History and Classification

Although the coincidence of xanthelasma with chronic jaundice and liver disease had been known for a long time no attempts were made to match these symptoms with a definite clinical entity Yet Addison and Gull[1] in 1851 already had published their classical paper containing a description of a case with skin xanthoma jaundice and a peculiar form of liver cirrhosis This early clinical description is of sufficient importance to be quoted verbatim for similarity to cases reported by Thannhauser and Magendantz[4] and MacMahon and Thannhauser[68] and quoted later in this section

Case of Eliza Parachute aged 33 of middle stature moderately nourished mother of six children catamenia regular Her present illness began in 1848 she attributes it to fright and to a blow received in the left groin whilst attempting to separate two men who were fighting Two days after this she became jaundiced and had from time to time severe paroxysmal pains about the hypochondria lasting for a day or two the liver being also enlarged and tender Four months after the commencement of the jaundice (August 4 1848) she was admitted into the hospital under the care of Dr Hughes She remained in until September 6 and left much in the same state she was in when admitted There was at this time nothing complained of beyond itching and irritation of the skin common in jaundice The present affection began after the jaundice had continued fourteen months when she again came under our care It first appeared in the hands spreading across the flexures of the joints of the fingers and palms Soon afterwards a yellowish patch of discoloration began near the inner canthus of the eyelid and then a precisely symmetrical one at the same part on the opposite eyelid These patches are very slightly raised and not obviously indurated they have extended very slowly At this time the patches on the face existed as above described Along the ridges bounding the flexures in the palm and about the joints of the fingers there were yellowish opaque irregular and somewhat raised lines About the thumb first joints of the fingers and the interior parts of the wrists there is a gradual transition to a tubercular prominence of the affected parts and some distinct tubercles exist on the elbow and knee

Menu for Hypercholesteremic Familial Xanthomatosis *

Grams of	CHO	PRO	FAT	TOTAL CALORIES
	500	55	50	26,0

BREAKFAST Juice of 2 oranges 1 sauce dish rolled oats with 1 table spoon sugar and 1 tablespoon butter 1 medium whole wheat muffin with 1 heaping tablespoon fruit jelly, 1 cup skimmed milk

MID MORNING ½ cup grape juice 3 crackers

LUNCH ¾ cup baked macaroni with ½ cup tomato sauce 1 table spoon bread crumbs and 1 tablespoon butter 3 leaves lettuce and rings green pepper 1 medium whole wheat muffin with 1 heaping tablespoon of marmalade 1 medium stuffed apple with meringue (2 teaspoons sugar 2 teaspoons raisins 1 egg white), 1 glass skimmed milk

MID AFTERNOON ½ cup of fruit juice 3 crackers

DINNER 2 medium baked potatoes with 1 tablespoon butter 1 sauce dish glazed carrots 1 sauce dish string beans 1 me dium whole wheat muffin with 1 heaping tablespoon jelly 1 large baked banana with 2 teaspoons sugar

BEFORE BED Juice of 1 orange with 1 teaspoon sugar

Ca P F and Vitamins A B C D G are adequate in this diet

It was shown by Roffo[3] that alcoholic extracts of eggplants (Solanum Melongena L) and of artichoke leaves lower the cholesterol in the serum of rats In normal man and in patients with familial hyper cholesteremic xanthomatosis extracts of artichokes did not lower, in the author's experience[4] , the cholesterol level of the serum

The advisability of giving thyroid in amounts ½ grain to 1 grain daily must be decided individually Caution also is advised in cases where angina symptoms indicative of coronary involvement are present or may occur during the treatment It is not possible to explain the effect of thyroid medication on the level of cholesterol in the blood However while it undoubtedly reduces the serum level of the cholesterol the main benefit derived from thyroid treatment is the fact that the patients complain less of fatigue or lack of energy

* This diet as well as all the other diets included in this chapter has been computed by Miss Frances Stern and Miss Helen Finkelstein of the Boston Dispensary

The first description of the eruptive form of xanthoma diabeticorum in a diabetic patient was also vividly presented in the same paper by Addison and Gull[4] The pupils of Addison at the Guy's Hospital reported the first anatomical findings in the liver bile ducts and arteries

Moxon[300] (1873) reviewed the case of a thirty-two year old man with severe jaundice of two years duration and two attacks of colic Xanthelasma were found on the palms scrotum, back, ears, cheeks and eyelids He died of hemorrhage due to a hepatic lesion The postmortem showed no gallstones but only hepatic cirrhosis

"The gall ducts throughout the organ were excessively wide so that on section of the liver their contents welled up in enormous quantity being a white clear fluid in strong contrast with the serum of the blood which was golden yellow These dilated gall ducts had xanthelasma looking patches within them that is white opaque patches The hepatic duct at the point of union of its two divisions was swollen from the pressure in it of a firm, tough matter making a little soft knot of the size of an almond around it and in its walls The microscope showed only fibrous scar tissue in the thickening

Futcher[141, 460] and Weidman[4 0] reported cases where the scar tissue almost completely occluded one of the bile ducts Granulomatous scar tissue may have resulted from xanthomatous patches lining the larger bile ducts Xanthomatous patches were found in the arteries especially the aorta in the trachea near the bifurcation and one in the capsule of the small spleen

Fagge[127] (1873) also described a case of vitiligoidea (It has since been given the more euphonious name of xanthelasma by Erasmus Wilson) This paper also contained a pathological report by Dr Howse The patient had been jaundiced continuously for seven years Xanthomatous patches were found on the eyelids, abdomen lips larynx and trachea The patient also had hepatic cirrhosis and an enlarged spleen with a considerable number of minute white grains within it The lungs and brain were normal Numerous yellow spots and patches were present in the left auricle aorta pulmonary artery and almost all the vessels

They were sharply defined and raised slightly above the level of the lining membrane of the vessel The nature of the growth appears to be essentially the same wherever it occurs whether in the mucous membrane on the tendons or on the skin It appears to be a kind of universal atheromatus change From wherever the sections are taken they show fine granular cells variously disposed amongst the fibrous tissues of the part affected In the other growths they undergo still further degenerative changes becoming

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converted into lumps of calcareous matter crystalline bodies etc Thus it would be a matter of indifference whether we should speak of the cutaneous disease as an atheroma of the skin or of the arterial affection as a xanthelasma of the aorta

In 1873 Pye Smith[313] also a physician at the Guy s Hospital described a third case including an autopsy A forty nine year old woman had suffered attacks of colic with intermittent jaundice over a period of two years Her urine however was always dark Xanthelasma were found only on both eyelids She died of an intercurrent severe erysipelas The postmortem examination revealed only one calculus in the gall bladder but the biliary ducts were found much dilated Patches precisely like those in the eyelids and hands were found on the surface of the spleen and in the mucous membrane of the dilated hepatic ducts The liver showed a slight degree of interstitial cirrhosis The patches in the ducts *looked just like atheroma in the artery with which condition indeed they* corresponded histologically

In 188- an English committee investigating xanthoma published a collection containing descriptions of twenty three similar cases with jaundice and xanthelasma (Hutchinson Sangster and Crocker[99]) The question of whether xanthoma occurs without liver disease was decided by the report of cases of xanthoma planum et tuberosum without jaundice The French author *Balzer[3] referring in 1884 to three patients with* liver disease and jaundice believed that he had proved an infectious etiology of the disease This assumption however was never confirmed

In 1890 Hardaway[281] reported a case of xanthomatous diathesis He suggested that xanthoma is a diathesis and that its relation to hepatic disarrangement was entirely secondary or in other words that the occurrence of jaundice during the course of the disease was the result of a deposition of xanthomatous tubercules in the liver This conception was not accepted Weber (1903) and Futcher[314] (1905) the latter reporting three cases from Osler s wards at Johns Hopkins believed that chronic obstruction of the bile duct is the primary cause of the development of xanthoma Futcher s opinion is surprising because of the following statement in his paper on section of the liver the bile ducts stood out everywhere looking like sclerotic arteries The walls of the bile ducts are considerably hypertrophied containing elastic fibers and the lumina are lined with a mass of lymphoid and plasma cells similar to those already described in the skin lesion

In 1911 Chvostek[83] pointed out that *jaundice and xanthelasma* are the result of the same disease that is they are due to a xanthomatou

involvement of the liver, which results in cirrhosis of this organ, and to a xanthomatous skin involvement visible as xanthelasma

Posner[310] in 1909 described a patient who, it was thought, had obstruction of the bile duct An operation did not reveal any obstruction Xanthoma of the skin developed after the operation The autopsy revealed hepatic cirrhosis and all kinds of xanthomatous changes in the organs

In the paper 'Hypercholesteremic Splenomegaly" Dyke[103] (1928) also reported the case of a patient with jaundice, xanthelasma planum et tuberosum, xanthomatous involvement of spleen and lymph nodes Buerger[9] described a fifty-five year old woman with extensive xanthoma tuberosum et planum jaundice and hepatic cirrhosis The following figures were found in the serum, extreme total cholesterol value of 2,575 mgm per cent 1 444 mgm per cent free and 1,131 mgm per cent esters A similar case with 1 0 0 mgm per cent of cholesterol was described by Weidman and Boston[4 6] The autopsy findings in these cases showed biliary cirrhosis xanthoma cells in the splenic and hepatic capsules also in a scar of herpes zoster like Hardaway's[183] case besides the extensive tuberous xanthoma of the skin The most important feature of this paper is not the occasional finding of a polyp of questionable adeno carcinoma of the empulla of Vater but the photograph of the histological picture of the wall of the gall bladder and the similarity of findings on the wall of the bile ducts, both showing extensive xanthomatous changes and xanthomatous scar tissue It was found that the common bile duct was enlarged to the size of an average thumb, and that the head of the pancreas was indurated However, no cause for the dilatation in the form of biliary obstruction could be demanstrated

A differentiation of the various forms of liver involvement in xanthomatous diseases was suggested by Thannhauser and Magendantz[4 7] and Thannhauser[440 68]

1) *Xanthomatous biliary cirrhosis* was established as a clinical entity with the following characteristic features
   (a) Jaundice of several years' duration The jaundice is of the obstructive type i e high values of bilirubin giving the direct bilirubin test of Van den Bergh
   (b) The serum shows extremely high values of total cholesterol (3-8 times those of normal) with a normal cholester-olester proportion (70 75 per cent of the total cholesterol) during the first phases of the disease In later stages the values of total cholesterol decrease and the cholesterol

ester proportion drops to 50 .5 per cent of the total cholesterol

(c) The lecithin content of the serum is outstandingly increased together with the high cholesterol values lecithin values 3 7 times higher than normal

(d) The appearance of permanent skin xanthoma of the tuberous and plain variety in the early phases of the disease

(e) The serum is transparent and not creamy because its content of neutral fat is low or normal

Skin xanthoma of the tuberous and plain variety are predominant around the eyes elbows buttocks knees and creases of the hand in xanthomatous biliary cirrhosis Tendon xanthoma and vascular atheromas or atheromas of the inner linings of the bile ducts sometimes appear simultaneously with this syndrome There is no involvement of the lungs lymph nodes brain or dura The liver tissue itself shows a special type of biliary cirrhosis Foam cells are not found in the liver parenchyma itself

2) *Hepatosplenomegaly due to hyperlipemia with secondary eruptive xanthoma* shows the following clinical characteristics

(a) An outstanding increase of neutral fat in the serum resulting in a creamy appearance The neutral fat values are 5-20 times those of normal (normal o oo mgm per cent

(b) The cholesterols and lecithins are only moderately increased (3 times those of normal) in comparison to neutral fat

(c) The patients are never jaundiced

Skin xanthoma of the tuberous variety may develop into tumors from the size of a pea to a walnut Although most commonly located on elbows buttocks knees and legs they may appear also on the mucous membranes of the mouth and on the ears simulating tophi In the liver and spleen rather rare foam cells are scattered diffusely in between the normal tissue architecture

3) *Hepatosplenomegaly in generalized form of eosinophilic xanthomatous granuloma synonymous with essential xanthomatosis of the normocholesteremic type lipid granuloma and eosinophilic granuloma* has the following clinical features

(a) Skin xanthoma of the disseminated type Enlargement of the liver and spleen diffuse lymphadenopathy lesions of lungs and osseous system

(b) These patients are never jaundiced

(c) The cholesterol, as well as the lecithin values in the serum are normal

Skin xanthoma of the disseminated variety, if present, are predominant around the neck and on the face and dispersed as solitary or conglomerated lesions on the trunk An especially characteristic location is in the axillae and bends of the knees and elbows where ridges and clusters are formed Their color is distinctive a lemon or maroon hue Hepatosplenomegaly in eosinophilic xanthomatous granuloma (essential xanthomatosis of the normocholesteremic type) may be associated with generalized lymphadenopathy as well as with involvement of the osseous system, brain and dura, lung pleura and the sockets of the teeth In contrast to xanthomatous biliary cirrhosis the hepatosplenomegaly of this disorder results from a systemic infiltrating granulomatous lesion consisting in its first phase of histiocytes, reticulum cells and eosinophiles and in later stages of aggregates of foam cells

* * * * *

Since the establishment by Thannhauser and Magendantz of the clinical syndrome of xanthomatous biliary cirrhosis (extremely high values of total cholesterol and lecithin but normal or low content of neutral fat in the serum associated with jaundice of the obstructive type of years duration) similar observations have been reported Chanutin and Ludewig[77] in a study of xanthomatosis associated with hepatic damage described a case in this group notwithstanding the fact that the patient was treated with arsphenamine injections Layani Laudat and Astruc[16, 47] observed a woman whose clinical and laboratory findings may suggest xanthomatous biliary cirrhosis This patient also had most severe destructive osteoarthritis Layani and coworkers, on the basis of a chemical examination of a joint biopsy, believed that this destructive joint disease is also of xanthomatous etiology Comfort Shepard and Snell published a most characteristic case of xanthomatous biliary cirrhosis This case had all the clinical features of this syndrome The analysis of the transparent serum showed the following figures total cholesterol 1 284 mgm per cent, cholesterolesters 740 mgm per cent total fatty acids 2 439 mgm per cent lecithin 2 225 mgm per cent fatty acids derived from neutral fat 75 mgm per cent neutral fat 78 mgm per cent calculated according to the formula of Thannhauser and Reinstein[479] Freda Herbert[191] observed a seven year old girl who had suffered from repeated attacks of jaundice The out-

standing features of this case were extensive cutaneous xanthoma xanthomatosis of the palm and creases of the hand enlargement of liver and spleen arrested growth and enormous increases in cholesterol cholesterolesters and lecithin in the blood plasma with little or no neutral fat in the serum The chemical analysis by Freda Herbert is the most careful one on record Her findings of low neutral fat in the serum are in conformity with our own analyses Low values for *neutral fat in the serum are as important for the diagnosis of xanthomatous biliary cirrhosis as are the extremely high values for cholesterol and lecithin* Freda Herbert hesitated to make the diagnosis of xanthomatous biliary cirrhosis in her case while the clinical liver function tests were normal at the time of observation In our experience the routine function tests are not of help in establishing the diagnosis in this syndrome since the liver functions are found normal with the routine tests at a time when the entire syndrome *(severe jaundice hypercholesteremia hyperlecithemia)* has been present Freda Herbert s description is of great importance for the seven year old girl is the youngest patient observed with xanthomatous biliary cirrhosis

Eusterman and Montgomery[122] from the wealth of material at the Mayo Clinic described a typical case of xanthomatous biliary cirrhosis in a paper entitled Disorders of the liver and extrahepatic biliary ducts associated with cutaneous xanthoma and hyperlipemia This publication also contained six cases with skin xanthoma and hyperlipemia associated with cirrhosis of the liver and four cases with skin xanthoma and hyperlipemia associated with cirrhosis of the liver secondary to mechanical obstruction of the common bile duct Eusterman and Montgomery applied the term hyperlipemia to signify the increase of total lipids especially cholesterols and lecithin in contrast to its customary usage which indicates an increase of neutral fat only in the serum The statement that the high figures for the total fatty acids usually are due to a high content of neutral fat is mostly true but misleading in these instances where the high figures *for total fatty acids are derived from* the extremely high cholesterolesters and phospholipids In fact if one subtracts from the reported total fatty acids the sum of fatty acids present in the cholesterolesters and lecithin in order to compute the fatty acids derived from neutral fat (glycerol esters) one arrives in Eusterman and Montgomery s own case to a negative figure for fatty acids derived from neutral fat i e extremely low values for neutral fat *Since this case (Case 1) of Eusterman and Montgomery does not show* an increase of neutral fat in the serum and because of the outstanding

increase of cholesterol and lecithin together with the occurrence of jaundice and skin xanthoma, the diagnosis of xanthomatous biliary cirrhosis seems appropriate

The value of neutral fat in the serum of the five other cases tabulated as liver cirrhosis and xanthoma cannot be computed, since only values for total fatty acids, lecithin and total cholesterol, but not cholesterol esters are reported It must be emphasized again that normal or low values for neutral fat are required for the diagnosis of xanthomatous biliary cirrhosis because high values for neutral fat (hyperlipemia with creamy serum and xanthoma formation) indicate an entirely different clinical syndrome, i e hepatosplenomegaly due to hyperlipemia with secondary eruptive xanthoma (see section on idiopathic hyperlipemia)

Hoffbauer Evans and Watson[199, 200] published an article on a case of xanthomatous biliary cirrhosis, in which the authors evaluated liver function tests and needle biopsies for diagnosis The 6 -year old female patient had the clinical characteristics of xanthomatous biliary cirrhosis At autopsy a bilirubin calcium stone was found in the common duct The serum bilirubin during the period of observation fluctuated between 4-9 mgm per cent The serum bilirubin certainly would have been higher if the stone had completely obstructed the common duct The authors state that "the stone found in the common duct was a secondary phenomenon of the disease since after seven years of jaundice the common duct might have been expected to be dilated had the stone been the causative factor in the production of cirrhosis" The autopsy of the liver showed the picture of a definite portal cirrhosis Xanthomatous formation of the larger bile duct which according to the suggestion of Thannhauser[4, 16, 4] should have been expected as the etiology of xanthomatous biliary cirrhosis was not found In a study of early biopsies and autopsy findings this author revised his opinion concerning the pathology of this syndrome[68] MacMahon and Thannhauser[3] demonstrated in the biopsies of the early stage of the disease a proliferative granulomatous lesion around the finest interlobular cholangioles and junction ducts extending to the periphery of the lobules and apparently obliterating some of these cholangioles At autopsy the liver in the final stages give the impression of a portal cirrhosis The inital characteristic pericholangiolotic changes are difficult to visualize in the end stage of the cirrhotic liver If such a damaged liver is seen only in the end stage without previous biopsy as in Hoffbauer Evans and Watson's case[199, 200] its pathogenetic development is difficult to unravel

A case of xanthomatous biliary cirrhosis with the characteristic features of this syndrome was reported by M C Gebhardt[illegible] who described a 37-year old female with jaundice of long duration extensive skin xanthoma total cholesterol of 1 193 mg per cent high total phospholipids low neutral fat and transparent serum

Pathology and Histology of Xanthomatous Biliary Cirrhosis Pericholangiolitic Biliary Cirrhosis with Tuberous and Plain Skin Xanthoma

Moxon[illegible] and Fagge[illegible] as well as Pye Smith[illegible] in 1873 reported the autopsy of three cases showing xanthoma of the skin and atheromatous changes on the inner lining of the arteries together with xanthoma formation on the lining of the bile ducts Pye Smith described the changes in the liver as showing a slight degree of interstitial cirrhosis The patches in the ducts looked just like atheroma in the artery with which condition indeed they corresponded histologically

Depending on these findings Thannhauser and Magendantz suggested that xanthoma formation of the larger bile ducts resulting in xanthomatous scar tissue may be the cause of the clinical syndrome designated as xanthomatous biliary cirrhosis It was their opinion that the development of the xanthoma of the skin as well as the xanthoma formation on the lining of the bile ducts is the expression of a systemic disease characterized by increased new formation of cholesterol and hypercholesteremia (hypercholesteremic xanthomatosis) The xanthomatous involvement of the large bile ducts and their partial obstruction was thought to be the primary event which resulted later in this special type of biliary cirrhosis

This opinion can no longer be maintained since their biopsies in early stages as well as autopsies of cases of xanthomatous biliary cirrhosis did not reveal xanthomatous changes of the lining of the bile ducts (Mac Mahon and Thannhauser [5]) The biopsies in the early stages showed a proliferative granulomatous lesion around the finest interlobular cholangioles and junction ducts extending to the periphery of the lobules and apparently obliterating some of the cholangioles Autopsy showed cobbling and portal cirrhosis in the liver in the final stages The initial characteristic pericholangiolitic changes are difficult to visualize in the end stage of the cirrhotic liver If such a cirrhotic liver is seen only in the end stage at autopsy without previous biopsy its pathogenetic

increase of cholesterol and lecithin together with the occurrence of jaundice and skin xanthoma, the diagnosis of xanthomatous biliary cirrhosis seems appropriate.

The value of neutral fat in the serum of the five other cases tabulated as liver cirrhosis and xanthoma cannot be computed, since only values for total fatty acids, lecithin and total cholesterol, but not cholesterol esters are reported. It must be emphasized again that normal or low values for neutral fat are required for the diagnosis of xanthomatous biliary cirrhosis because high values for neutral fat (hyperlipemia with creamy serum and xanthoma formation) indicate an entirely different clinical syndrome, i.e. hepatosplenomegaly due to hyperlipemia with secondary eruptive xanthoma (see section on idiopathic hyperlipemia).

Hoffbauer, Evans and Watson[109, 60] published an article on a case of xanthomatous biliary cirrhosis in which the authors evaluated liver function tests and needle biopsies for diagnosis. The 62-year old female patient had the clinical characteristics of xanthomatous biliary cirrhosis. At autopsy a bilirubin calcium stone was found in the common duct. The serum bilirubin during the period of observation fluctuated between 4.9 mgm. per cent. The serum bilirubin certainly would have been higher if the stone had completely obstructed the common duct. The authors state that "... the stone found in the common duct was a secondary phenomenon of the disease since after seven years of jaundice the common duct might have been expected to be dilated had the stone been the causative factor in the production of cirrhosis." The autopsy of the liver showed the picture of a definite portal cirrhosis. Xanthomatous formation of the larger bile duct which according to the suggestion of Thannhauser[4, 16, 4] should have been expected as the etiology of xanthomatous biliary cirrhosis was not found. In a study of early biopsies and autopsy findings this author revised his opinion concerning the pathology of this syndrome.[68] MacMahon and Thannhauser[68] demonstrated in the biopsies of the early stage of the disease a proliferative granulomatous lesion around the finest interlobular cholangioles and junction ducts extending to the periphery of the lobules and apparently obliterating some of these cholangioles. At autopsy the liver in the final stages gave the impression of a portal cirrhosis. The initial characteristic pericholangiolotic changes are difficult to visualize in the end stage of the cirrhotic liver. If such a damaged liver is seen only in the end stage without previous biopsy, as in Hoffbauer, Evans and Watson's case[109], its pathogenetic development is difficult to unravel.

the periphery of the lobules suggested a moderate degree of liver cell regeneration (Fig 45 Case XX)

In one of the four biopsies the damage to the parenchyma was greater than in the others In this biopsy in contrast to the other three there were fields in which the inflammatory reaction had cut deeply into the centers of the lobules (Fig 32 Case XVI) In this way central veins became isolated from the body of the parent lobules (Fig 46 Case XX) These islands in turn seemed to melt away to become replaced by inflammatory granulation tissue (Figs 47 48 Case XX) In one area an entire lobule had been destroyed and was now substituted by fibrous tissue

The one fundamental histological finding common to all four biopsies was a chronic inflammatory reaction in the interstitial portal areas It began as chronic pericholangiolitis and spread over into the peripheral zones of the adjacent lobules

Autopsy Findings

To understand the development of the different types of cirrhosis it is necessary to know these types in all their stages A study of this material afforded the opportunity to compare adequate sections from the livers of patients during life with sections obtained months and years later

Grossly the livers of the two patients who came to autopsy were large firm and cobbled They weighed 2 600 and 2 800 grams respectively On section the texture was coarse and bile stained There were no depositions of cholesterol in the mucosa of the gall bladder or in any of the bile ducts There were no concretions and finally there was no suggestion of any type of extrahepatic biliary obstruction

The histology was much more complex and confusing than in the earlier biopsies In a few areas the central veins central zones and mid zones were still recognizable but for the most part the normal lobular pattern now was severely distorted Bands of fibrous tissue divided the parenchyma into irregular and uneven nodules The portal areas were composed of wide and communicating bands of connective tissue that extended deeply into the parenchyma and not infrequently replaced whole lobules

The parenchyma was composed of irregular cords of liver cells separated by edema fluid dilated sinuses and fibrous tissue (Figs 33 Case XVI 34 Case XVI) Here and there the Kupffer cells were large

development would be difficult to unravel and its classification would be uncertain MacMahon and Thannhauser believe, on the basis of the early biopsies and autopsies of cases of the clinical syndrome 'xanthomatous biliary cirrhosis', that the histopathological findings of these cases justify the assumption of a special type of cirrhosis, which they designate anatomically as pericholangiolitic biliary cirrhosis with tuberous and plain skin xanthoma'

Early Biopsies*

In *early biopsies* in the portal areas there were chronic proliferative and exudative inflammatory reactions which were most concentrated about the junction ducts (canals of Hering) and terminal bile ducts (interlobular bile ducts or cholangioles) at the periphery of the lobules (Figs 40 41 Case XIX, 27, 28 Case XVI) The portal areas were larger broader and longer than usual and often fused with one another to form rings of perilobular fibrosis Inflammatory granulation tissue extended into the periphery of the lobules It blocked canaliculi destroyed liver cells and collapsed many sinuses (Fig 29, Case XVI)

The larger bile ducts were patent and empty The small interlobular bile ducts were very difficult to find and in many of the portal areas there were none The junction ducts, which in a normal liver are so inconspicuous were numerous elongated, branching and tortuous Some were dilated and filled with bile, others were collapsed and empty None of the ducts contained leucocytes although several types of inflammatory cells including lymphocytes plasma cells histiocytes neutrophiles and occasionally eosinophiles richly infiltrated the surrounding granulation tissue

The lobular pattern of the liver was well preserved and most central veins bore a normal relationship to the surrounding liver parenchyma Large and sometimes lamellated bile casts were fairly numerous within the lobules (Fig 43 Case XIX) These distended the canaliculi and often damaged the bordering liver cells For the most part the liver cells were healthy (Fig 31 Case XVI) few contained fat droplets and some lying in the field of inflammatory reaction about the portal areas showed degeneration and necrosis There were few mitoses (Fig 30 Case XVI) and the presence of closely packed clusters of small cells near

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* The author is indebted to Dr H Edward MacMahon Professor of Pathology at Tufts Medical School Boston Massachusetts for the histological pictures and accompanying legends

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The histology was much more complex and confusing than in the earlier biopsies In a few areas the central veins central zones and midzones were still recognizable but for the most part the normal lobular pattern now was severely distorted Bands of fibrous tissue divided the parenchyma into irregular and uneven nodules The portal areas were composed of wide and communicating bands of connective tissue that extended deeply into the parenchyma and not infrequently replaced whole lobules

The parenchyma was composed of irregular cords of liver cells separated by edema fluid dilated sinuses and fibrous tissue (Figs 33 Case XVI 34 Case XVI) Here and there the Kupffer cells were large

swollen and filled with lipoid, and nests of these occasionally distended the sinuses and compressed the adjacent trabeculae There was much bile stasis with bile in the canaliculi liver cells and sinuses

The larger bile ducts were collapsed and empty (Fig 4- Case XIX) (biopsy) The terminal ducts were inconspicuous and embedded in fibrous tissue In none of the ducts was there either an inflammatory exudate or any evidence of foam cells

The large size of the liver, the extensive fibrosis the fragmentation of some lobules and the total loss of others the nodules of regenerated liver tissue, the compression and interruption of liver cords by fibrous tissue the patchy bile stasis the intralobular lipoid deposition and finally, the presence of a still active chronic inflammatory reaction in portions of the interstitial tissue all combined at this late stage to form a very confusing histological picture If such a damaged liver were to be seen for the first time without an earlier biopsy its pathogenesis would be difficult to unravel and its classification would be uncertain In this late stage it could easily be misinterpreted as an advanced stage of Laennec's cirrhosis

Moxon[300] and Fagge[1] in 1873 reported the autopsy findings of two cases showing xanthoma of the skin with either atheromatous changes on the inner linings of the arteries or xanthoma formation on the linings of the bile ducts Pye-Smith[313] in the same year described a third case of cutaneous xanthomatosis in which the patient showed cholelithiasis and dilation of the extrahepatic biliary ducts The liver of this patient showed changes suggesting a slight degree of interstitial fibrosis Of this particular case Pye Smith wrote the patches in the ducts looked just like atheroma in the artery with which condition indeed they corresponded histologically

On this evidence Thannhauser and Magendantz suggested that xanthoma formation of the bile ducts resulting in xanthomatous scar tissue might be the cause of the clinical syndrome which they had designated as xanthomatous biliary cirrhosis It was their opinion that the development of the xanthoma of the skin as well as the xanthoma formation within the bile ducts was the expression of a primary systemic disease characterized by an increased formation of cholesterol with hypercholesteremia (hypocholesteremic xanthomatosis) The xanthomatous involvement of the large bile ducts and their partial obstruction was thought to be the primary event which resulted later in this special type of biliary cirrhosis (xanthomatous biliary cirrhosis)

This opinion can no longer be maintained since their biopsies taken

during the early stages as well as the autopsies years later on cases of xanthomatous biliary cirrhosis did not reveal the anticipated xanthomatous changes in the linings of the bile ducts. The biopsies in the early stages showed a proliferative and exudative inflammatory reaction about the smallest of the interlobular cholangioles and junction ducts extending into the periphery of the lobules. The autopsies showed cobbling of the liver, marked enlargement of the liver and advanced cirrhosis. At this late stage the initial and characteristic pericholangiolitic changes were difficult to see. When such a cirrhotic liver is seen without previous biopsy an accurate diagnosis would be difficult and its pathogenesis would be uncertain. It is now believed on the basis of biopsies and autopsies of cases showing the clinical syndrome of xanthomatous biliary cirrhosis in the absence of any extrahepatic biliary obstruction that the histopathological findings in the liver justify the recognition of a special type of cirrhosis which may be designated anatomically as pericholangiolitic biliary cirrhosis.

Xanthomatous biliary cirrhosis is a clinical syndrome and this name will be used in the text of this chapter. Periocholangiolitic biliary cirrhosis is the anatomical designation of the histological findings in this clinical syndrome. In the text this syndrome will be referred to as xanthomatous biliary cirrhosis.

Etiology

Addison's pupils Moxon[306], Fagge[177] and Pye Smith[343] reported autopsies of their three cases which showed xanthoma of the skin and atheromatous changes on the inner lining of the arteries as well as xanthoma formation on the lining of the larger bile ducts. Pye Smith described the changes in the liver as revealing a slight degree of interstitial cirrhosis; the patches in the bile ducts looked just like atheroma in the artery, with which condition indeed they corresponded histologically.

Thannhauser and Magendantz[477] and this author in the first edition of Lipidoses were not at that time in a position to report autopsy findings of their own cases. Depending on the autopsies of Moxon, Fagge and Pye Smith, they suggested xanthoma formation of the larger bile ducts with resultant obstructive xanthomatous scar tissue as the cause of xanthomatous biliary cirrhosis. It was Thannhauser's opinion that xanthoma formation of the skin as well as xanthoma formation of the lining of the bile duct in xanthomatous biliary cirrhosis is the primary disorder

and one of the features of essential xanthomatosis of the hypercholesteremic type The ensuing biliary cirrhosis was thought to be secondary to the xanthomatous involvement of the bile ducts

This opinion can no longer be maintained, since autopsies meanwhile have been performed in three cases none of them showing xanthomatous changes of the lining of the bile ducts Liver biopsies in the early stages of the disease and autopsies in the terminal cirrhotic stage however revealed fibrotic changes in and around the finest interlobular bile capillaries and junction ducts, while the larger bile capillaries are patent Bile stasis is present only in the interlobular capillaries and in the liver cells themselves the larger ducts are patent and not involved (see section on Pathology and Histology)

On the basis of these findings xanthomatous biliary cirrhosis now may be considered as a primary liver disorder with secondary development of skin xanthoma and atheroma formation of the inner lining of the arteries and possibly, in rare cases of the bile ducts

It is however, still an open question as to whether the enormous accumulation of cholesterols and lecithin in the serum at the beginning of this disorder is due only to the obstructive fibrotic lesions of the interlobular cholangioles or whether in addition an increased formation of these substances in the liver cells must be assumed to explain the outstanding features of this syndrome in its early stage, namely, hypercholesteremia and hyperlecithinemia in a proportion unparalleled in any other disease

The following considerations and observations favoring the assumption of an increased cholesterol and lecithin synthesis in the early stages of xanthomatous biliary cirrhosis may be brought forth

(1) An increase of cholesterols and lecithin in the serum to values 5-10 times those of normal is found at the beginning despite the fact that the bile flow is never completely interrupted and bile is always present in the intestines as evidenced by duodenal drainage and by the presence of urobilinogen and urobilin in feces and urine In cases of complete obstruction of the large bile duct (surgical obstruction of the common duct stone new growth) all bile constituents like cholesterol and lecithin are normally formed but retained in the serum The cholesterol and lecithin values in the serum, however usually are not higher than about 2-4 times those of normal In complete obstruction of long duration the cholesterol accumulation begins gradually, in the disorder under discussion the highest values for cholesterol are found already at the beginning of the disease

(2) Permanent tuberous skin xanthoma also appear early in the disease together with the increase of cholesterol and lecithin in the serum In cases of complete mechanical obstruction of the large bile duct, however skin xanthoma usually do not develop In the few cases, where skin xanthoma were observed after surgical obliteration of the common duct the xanthoma were transient disappearing after the bile flow was restored by a plastic operation[7] The incidence of skin xanthoma is not mentioned in a report of 44 cases of complete obstruction of the duct (157 neoplastic obstruction 42 cases of stone obstruction and 39 cases of surgical obliteration)[161]

(3) The *figures of continuous serum analyses during three years* of illness in the case of *D I M* (see Case XVI) are highly significant for the question under discussion At the beginning this patient had 1 460 mgm per cent total cholesterol in her serum Despite the complete restriction of animal cholesterol from her diet (exogenous cholesterol) the level of serum cholesterol remained at about 800 mgm per cent for two and a half years Apparently it was not possible to reduce the abundant endogenous formation of cholesterol during this dietary period until in the final months it fell to 444 mgm per cent and was four weeks before her death 258 mgm per cent Simultaneously with the decrease of the serum cholesterol the patient developed a cough and a spiking form of fever The autopsy revealed an acutely progressing tuberculosis of the lungs and miliary dissemination of this disease The greatest part of the liver tissue was replaced by tuberculous nodes The fibrotic changes around the finest bile capillaries were as evident at the autopsy as in the early biopsy The retention of bile and therefore also of cholesterol persisted until the end If the cholesterol retention alone were the only cause of the enormous serum cholesterol values these high figures should have persisted until her death The incidence of miliary dissemination and the consecutive replacement of liver tissue by tuberculous nodes acted like an experiment by demonstrating that the liver cells had a substantial share in producing the accumulation of cholesterol in the serum in this disorder

(4) The cholesterol and lecithin excretion into the bile and the release of newly formed cholesterol and lecithin from the liver into the blood stream seem to be functionally related Cholesterol excretion into the bile normally is limited to a narrow range and varies but little The physiological concentration of cholesterol in the bile is low much lower than in the serum[13] For this reason increased cholesterol formation in the liver is bound to cause a considerable accumulation of cholesterols

in the serum present mainly as cholesterol ester as long as ... are anatomically and functionally intact If in addition to ... disturbance of increased cholesterol and lecithin formation ... the bile capillaries undergo fibrotic changes the accumul... substances in the serum will reach tremendous proportions ... xanthomatous biliary cirrhosis



Fig 22 Xanthoma planum et tuberosum on the face and around the eyelids and the papulo pustular form on the face (case XV II 1)

These considerations favor the suggestions of Thannhauser[4, 43] that the marl ed accumulation of cholesterol and lecithin in the serum as obser\ ed at the outset of \anthomatous biliar\ cirrhosis is not only the result of a retention of bile but also the outcome of t\\ o incidents namely (1) increased cholesterol and lecithin production and (2) an inadequate



Fig 23 Xanthoma planum on the palms and creases (case XV H L)

cholesterol and lecithin e\cretion The latter statement is definitel\ pro\ en b\ the histological demonstration of obstructi\ e changes in the smallest bile capillaries On the other hand the assumption of h\per-production of cholesterol and lecithin in \anthomatous biliary cirrhosis

in the serum, present mainly as cholesterol ester as long as the liver cells are anatomically and functionally intact If, in addition to the functional disturbance of increased cholesterol and lecithin formation, the roots of the bile capillaries undergo fibrotic changes, the accumulation of these substances in the serum will reach tremendous proportions as seen in xanthomatous biliary cirrhosis



Fig 22 Xanthoma planum et tuberosum on the face and around the eyelids with the papulo pustular form on the face (case XV H L)

These considerations favor the suggestions of Thannhauser[4, 13] that the marked accumulation of cholesterol and lecithin in the serum as observed at the outset of xanthomatous biliary cirrhosis is not only the result of a retention of bile but also the outcome of two incidents namely (1) increased cholesterol and lecithin production and (2) an inadequate



FIG 23 Xanthoma planum on the palms and creases (case XV H L)

cholesterol and lecithin excretion The latter statement is definitely proven by the histological demonstration of obstructive changes in the smallest bile capillaries On the other hand the assumption of hyperproduction of cholesterol and lecithin in xanthomatous biliary cirrhosis

remains a hypothesis suggested on the basis of laboratory findings and clinical considerations Clinical experience teaches us that in cases of complete bile obstruction as well as in epidemic hepatitis skin xanthoma almost never develop while in xanthomatous biliary cirrhosis skin xan



Fig 4 Xanthoma tuberosum on both elbows (case XV H L)

thoma appear early in the disease and persist during its entire course despite the fact that the bile flow is never completely interrupted

Clinical Cases

Case XV H L * a thirty two year old housewife born in Vienna was admitted to the Colorado General Hospital in November 1935 The

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patient complained of jaundice and weakness of four years duration Two years previously yellowish plaques had appeared over her entire body especially on her face and in the creases of her hands and feet

The patient stated that she had been in comparatively good health until June 1931 when she first noticed that her eyes were yellow Shortly afterward she observed that her skin also had become yellow Her urine was highly colored The stools were grayish The jaundice which gradually increased in intensity was accompanied by severe itching In September of the same year a physician advised a gallstone operation which was refused The patient's weight in the meantime had dropped from 160 to 1 5 pounds

In March 193 the patient consulted another physician who told her that she had an obstruction of the gall ducts and recommended an operation The patient again refused to follow this advice The jaundice by this time had increased in severity The itching was almost intolerable The next month she consulted two more physicians whose diagnosis and recommendations were the same as those given previously The patient in addition was told that she had a large liver

Although there was now some variation in the intensity of the jaundice and the itching had lessened the patient still complained of great weakness Xanthelasma palpebrarum were observed on both eyelids (Fig 21) In May 1933 she underwent an operation The spleen was removed No gallstones were found but only a narrowing of the common bile duct There was however no subsequent change in her condition

At this time the patient also noticed the appearance of yellowish deposits in the skin Although the onset was gradual the distribution was diffuse These deposits were first observed in the creases of the hands (Fig 23) They were found later on the face and on all the extremities including both elbows simultaneously (Fig 24)

The patient was seen again by a doctor in August 1934 The yellowish plaques now were enlarged patches prominently raised above the surrounding skin They were found on the anterior and extensor surfaces of the elbow elbow tips and buttocks The plaques in the creases of the palmar surfaces of both hands were about mm wide and slightly raised above the skin

About the middle of 1934 the patient became sick with a high fever and some delirium There also was an increase in jaundice In May 1935 she was given a number of fever treatments at the Colorado Psychopathic Hospital Her condition however showed no improvement

When the patient was admitted in May 1935 to Dr Waring's service at the Colorado Hospital her entire body was jaundiced The dusky brown color tinged with yellow was diffuse and uniform There were no distinct patches of pigment The mucous membranes were not discolored Large patches of xanthelasma were present on both eyelids and along the inner

remains a hypothesis suggested on the basis of laboratory findings and clinical considerations Clinical experience teaches us that in cases of complete bile obstruction as well as in epidemic hepatitis skin xanthoma almost never develop, while in xanthomatous biliary cirrhosis skin xan



Fig 24 Xanthoma tuberosum on both elbows (case XV H L)

thoma appear early in the disease and persist during its entire course despite the fact that the bile flow is never completely interrupted

Clinical Cases

Case XV H L * a thirty two year old housewife born in Vienna was admitted to the Colorado General Hospital in November 1935 The

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Blood examination showed the following figures hemoglobin 10 grams erythrocytes 3 million per cu mm leukocytes 1 650 polymorphonuclears 80 per cent lymphocytes 14 per cent monocytes 4 per cent eosinophiles 2 per cent The blood sedimentation was 0 per cent for one half hour 40 per cent for 1 hour The electrocardiogram showed slight left axis deviation Basal metabolism rate was plus 6 The urine contained bile

Blood chemistry Sugar (dextrose) 84 mgm per cent total non protein nitrogen 33 total cholesterol 400 calcium 10 60 Van den Bergh test 2 66 mgm bilirubin per 100 ml blood direct reaction Icterus index 2 Fragility of red cells normal

Biopsy Removal of a xanthoma from the dorsal surface of the left elbow (November 1935) (Analysis of tissue by the Biochemical Institute University of Denver)

	% by weight of fixed tissue
Total cholesterol (normal 0 1–0 3 mgm %)	1 31%
Free cholesterol	None
Cholesterol esters	1 31%
Total phospholipids	0 117%

Case XVI D L M A forty four year old French Canadian woman was admitted to the Joseph H Pratt Diagnostic Hospital in November 1939 The patient stated that she had been perfectly well up to 1937 when she first noticed icterus of her scleræ and skin Although at that time she had no abdominal pain she became severely nauseated and vomited every morning She developed anorexia and lost about thirty pounds within four months She observed also severe pruritus of the skin especially of her arms She had no fever or chills Her stools were clay colored Her urine was a deep orange

In May 1938 she had been hospitalized at the Boston City Hospital for ten days She was placed on a liquid diet The patient stated that the jaundice of her scleræ and skin decreased considerably After her discharge she faithfully kept to her diet However three months later jaundice of her skin and scleræ again developed There was only slight pruritus The patient did not have fever chills or abdominal pain Her stools again became clay colored Her urine was presistently deep orange Although the jaundice varied in intensity it was present to some extent all the time

In January 1939 the patient noticed a yellowish discoloration and elevations along the creases of both palms These lesions were progressive In June 1939 she observed a small flat yellowish plaque along the inner canthæ of both eyes These plaques progressed rapidly involving the upper and lower eyelids As far as the patient knew there were no other yellowish spots nodules or papulo pustular eruptions on her body

canthæ (Fig -) Yellowish nodules raised about 3 mm above the skin were found on both palms, along practically all the flexor creases A large hyperkeratotic mass of the same character was seen on the extensor surface of the elbow (Fig 4) Many similar nodules were distributed along the dorsum of the foot especially around the toes In addition to the plain and tuberous xanthoma there was a nodular pustular eruption all over the body (Figs and 5) The papules were excoriated by scratching The heart was normal

From the fall of 1935 the patient gradually lost ground She had a slight intermittent fever There were numerous persistent nasal hemorrhages The first of these which had occurred in 1934 lasted about ten hours It is estimated that one pint of blood was lost Subsequent nose bleeds of more



Fig 25 Xanthoma tuberosum et planum and papulo pustular eruptions on both legs (case XX H L)

or less severity occurred about every six weeks The epistaxes which lasted from six to ten hours were controlled with difficulty The patient did not bruise easily and apparently did not have any petechial spots She showed marked susceptibility to respiratory infections which were severe and prolonged With one of these she had acute suppurative otitis media on the right side The patient died in July 1936 apparently of a typical coronary occlusion

X rays taken in May 1935 revealed no changes in the bones skull chest, pelvis hands or feet

dullness was not enlarged by percussion The rate was 76 per minute and the rhythm was regular No murmurs were heard The vessels were not arteriosclerotic The radials were equal and synchronous Blood pressure 135/85

The abdomen was soft without tenderness or rigidity The liver which was markedly enlarged especially on the right side of the abdomen extended up into the left hypochondrium The spleen was not definitely palpable but enlarged by percussion No other masses were felt

There was a small yellowish elevated nodule about 5 mm in diameter over the ankle of the right foot A small wide yellowish plaque of mm and another of pinpoint area were observed in the right antecubital space No nodules were found on the extensor surfaces of the elbows and knees There were slightly elevated yellowish deposits a few mm in width along most of the flexor creases of both palms These were most marked at the metacarpophalangeal creases of the thumb In some interspaces they extended almost to the dorsum of the hand The reflexes were normal

X ray examination The liver was extremely enlarged The spleen appeared at this time to be within normal limits There was no x ray evidence of esophageal varices

Laboratory data Urine amber color cloudy reaction acid specific gravity 1 007 slightest possible trace of albumin negative sugar normal urobilinogen rare red and white cells Blood sedimentation rate was 86 mm at the end of one hour by the Westergren method Hemoglobin 69 or 9 5 grams red blood cells 3 10 000 white blood cells 11 450 color index 1 05 differential count showed 74 polymorphonuclears 1 bands eosinophiles 1 basophiles 19 lymphocytes and 3 monocytes The smear showed some anisocytosis macrocytosis and microcytosis The platelets appeared normal

Blood chemistry icterus index 63 Bilirubin direct 6 6 indirect 6.6

Total cholesterol		1460 mgm
Free cholesterol		155
Cholesterol esters	(90 of total)	1305
Total phospholipids		300
Sphingomyelin		150
Cephalin		30
Lecithin		120
Total fatty acids		1950
Fatty acids derived from neutral fat		0
Neutral fat		0
Bile acids		5
Carotene		negligible

The patient complained of tiredness weakness and listlessness After a fall three to four weeks before admittance to hospital she had constant pain in the lower lumbar region and a sharp pain between the shoulder blades radiating around the left chest wall to the left inframammary region This pain which came on in the evening was not related to exertion exposure to cold air or to the eating of heavy meals It was not relieved by rest The patient had no headaches or sinus trouble Her vision had been blurred She has had no diplopia She has no ear or nose symptoms Her teeth were in poor condition For the previous two to three years she had a cough producing yellowish whitish sputum She had no hemoptysis or pleuritic pains no exertional dyspnea orthopnea ankle edema or angina pectoris There had been no recent nausea or vomiting Her appetite had been improving She took mineral oil every morning prophylactically However, she was not constipated and did not have any diarrhea Her stools were clay colored normally formed most of the time and not frothy or foul in odor She had nocturia one to two times a night but no dysuria hematuria or pyuria Her urine at this time was persistently deep orange in color The patient complained of recent nervous feelings She had noticed a tingling sensation in both hands and wrists for over a year

Her habits were regular She ate three times a day She had meat in the form of liver and steaks as part of her antianemic diet and fruit juices for liver trouble She had insomnia In the past she worked as a night club hostess for three years and drank more than her share of liquor She had not had practically any alcohol in the previous eighteen months

The patient s father had died of heart trouble at the age of fifty The mother died of carcinoma of the uterus at the age of fifty two The mother s father had died of carcinoma of the stomach The mother s sister had diabetes There was no history of xanthomatosis in the family

Physical examination showed a small deeply jaundiced woman with temperature 97° F The skin over the arms was brownish colored There was also a combination of lemon yellowish and brownish jaundice on the palms A small nodule was found in the right occipital region of the scalp Rather extensive xanthelasma were present in the inner canthi and along both the upper and lower lids Those in the upper lid were more marked measuring 3½ to 4 cm in length and about ½ cm in width They were also elevated one to two mm above the level of the skin The conjuctivæ were not pale Several small irregular nodules were found in the right inferior palpebral conjuctivæ The scleræ were deeply jaundiced The fundi were not remarkable and there was no lipemia retinalis The mucosa of the hard palate was jaundiced No yellowish nodules were seen on the buccal or pharyngeal mucosa

The lungs were normal The apex impulse of the heart was felt 9 cm to the left of the midsternal line in the fifth interspace The area of cardiac

dullness was not enlarged by percussion The rate was 76 per minute and the rhythm was regular No murmurs were heard The vessels were not arteriosclerotic The radials were equal and synchronous Blood pressure 135/85

The abdomen was soft without tenderness or rigidity The liver which was markedly enlarged especially on the right side of the abdomen extended up into the left hypochondrium The spleen was not definitely palpable but enlarged by percussion No other masses were felt

There was a small yellowish elevated nodule about 3 mm in diameter over the ankle of the right foot A small wide yellowish plaque of [illegible] mm and another of pinpoint area were observed in the right antecubital space No nodules were found on the extensor surfaces of the elbows and knees There were slightly elevated yellowish deposits a few mm in width along most of the flexor creases of both palms These were most marked at the metacarpophalangeal creases of the thumb In some interspaces they extended almost to the dorsum of the hand The reflexes were normal

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Blood chemistry icterus index 63 Bilirubin direct 6 6 indirect 6 6

Total cholesterol		1460 mgm %
Free cholesterol		155
Cholesterol esters	(90 % of total)	1,305
Total phospholipids		300
Sphingomyelin		150
Cephalin		30
Lecithin		1[illegible]0
Total fatty acids		1970
Fatty acids derived from neutral fat		0
Neutral fat		0
Bile acids		5
Carotene		negligible

After a cholesterol free diet

Total cholesterol		1140	mgm %
Free cholesterol		406	"
Cholesterol esters	(60% of total)	734	"
Icteric index		70	"
Bile acids		8	"

The patient was discharged from the hospital with a diet almost free of animal cholesterol and low in animal fats Vegetable fats like olive oil and peanut oil were allowed

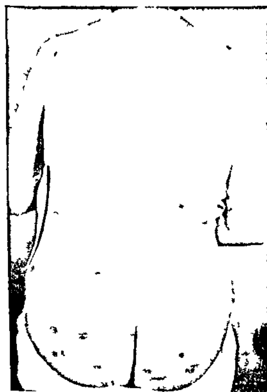


Fig 6 Papulo pustular eruption on the back

Follow up Notes on Case XVI *1-1-40* —The patient reported that she kept to her diet The jaundice seemed unchanged *Liver* four fingers below the costal margin firm and smooth surface *Spleen* definitely enlarged and palpable two fingers below the left costal margin Constant itching of skin For chemical analysis of serum see Table VI

6 1-40 —The skin xanthoma did not change although the patient adhered rigidly to her diet Liver enlargement was not diminished Spleen was felt two fingers below the left costal margin The patient complained of pain

in her stomach two to four hours after she ate pain which awakened her in the early morning hours As she was already on a vegetarian diet low in fat but high in carbohydrates no special diet change was made For blood chemistry see Table VI

- 7 41—Condition was unchanged For blood chemistry see Table VI

7 - 41—*X ray showed a double ulcer of the duodenum* Stool examination for occult blood was slightly positive Patient had profuse vaginal bleeding the previous week Gynecological examination showed vaginal polyp and fibromatous uterus For blood chemistry see Table VI Cholesterol free diet was continued

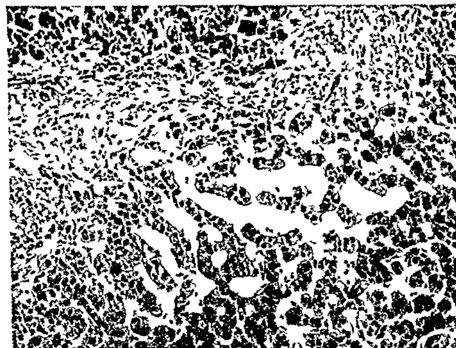


FIG 27 Liver from biopsy case XVI This field was selected to show a portion of the peripheral zone of a lobule together with an inflamed and thickened portal area It shows an extension of the inflammatory process into the lobule with compression of some sinuses and dilation of others

11 14 41—Because of increasingly constant pain an exploratory laparotomy was performed by Dr F H Clute (11 0 41) which revealed a double duodenal ulcer It was not resected Postoperative course was uneventful There was no bleeding At this time a liver biopsy was taken See Figs 7 3 for findings

1 7 4.—Abdominal discomfort from the ulcer continued The patient believed that she had contracted an upper respiratory infection a few weeks previously She coughed and produced a fair amount of whitish mucous sputum

7-5 4.—Cough and sputum were less Her main complaint now was the itching of the skin Liver and spleen still were enlarged Jaundice and skin xanthomata were unchanged For blood chemistry, see Table VI

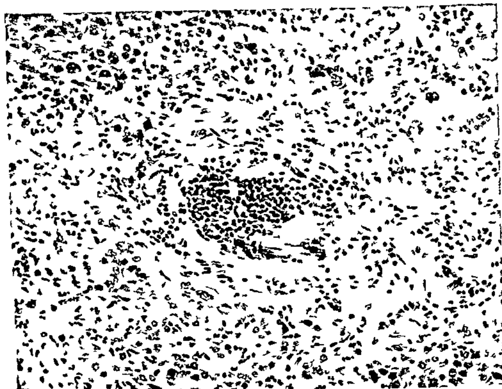


Fig 28 Liver from biopsy case XXI This field was selected to show an inflamed and widened portal area There is a rich cellular infiltration There is an increase in inflammatory granulation tissue and there is an extension of this inflammatory reaction into the peripheral zones of the lobule No bile ducts are visible in this field but liver cells are so compressed that they resemble terminal cholangioles The only suggestion of a portal vein is the presence of several compressed and slit like endothelial lined spaces

1. 10 4.—Patient had lost considerable weight (10 to 15 lbs) in the past two weeks She developed a high temperature running up to 103 F which continued from that time X ray pictures of the lung unfortunately were not taken

1-16 43—The patient was hospitalized again because of her extreme weakness and high temperature *Lung*—Over both lungs fine moist con-

sonitin_ rales were heard there was no dullness The patient was believed to have pneumonitis The sputum was not examined for tubercle bacilli X rays of the lung were not taken Liver and spleen were greatly enlarged There were no ascites no evidence of ankle edema Xanthoma and jaundice were unchanged Spider veins were noted on several places on her skin For blood chemistry see Table VI The patient became progressively weaker and died on 7 41 *Up to her death she was conscious* and was *not in a* hepatic coma For final blood chemistry see Table VI

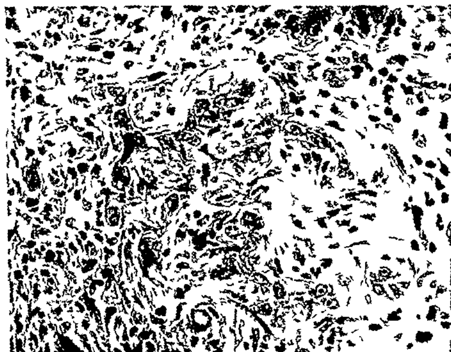


Fig 9 Liver from biopsy case XVI This is a higher power magnification of a field at the periphery of a lobule It shows the increase in fibrous tissue extending into the lobule surrounding and compressing cords of liver cell Neither the sinuses nor the sinus endothelium is recognizable The sinuses are now filled with inflammatory granulation tissue

Pathology (Case XVI)—The biopsy specimen received in November 1941 from Case XVI was wedge shaped and measured 1 5 × 1 × 0 8 cm It included capsule and underlying liver tissue There was no gross thickening or irregularity of the surface Many sections were made and each was entirely free of subcapsular fibrosis a condition commonly seen in blocks of liver taken from the gall bladder area In each section between 50 and 100

TABLE VI

	Normal	11 27 39	1 1 40	6 1 40	2 7 41*
Total cholesterol	150 60 mgm /	1,460.0 mgm /	1 140 0 mgm /	840 0 mgm /	1 040.0 mgm /
Free cholesterol	40 70	155 0	406 0	250.0	300 0
Cholesterol present as esters	0 75 of total cholesterol	1 305 0	734 0	590 0	740 0
Total phospholipids	150 50 mgm /	2 300 0		1 5, 0	
Cephalin	10 30	30.0			
Lecithin	140 2 0	2 1 00			
Total fatty acids	200 450	1 970 0			
Neutral fat fatty acids	0 150	0			
Neutral fat	0 150	0			
Bile acids	0 2	5.0	8.0	6.44	
Bilirubin (direct)		6 60		3 6	
Bilirubin (indirect)		6 60		5.4	

	7 22 41*	11 14 41*	1 7 42*	7 5 4	1 16 43†	27 3 death
Total cholesterol	6,00 mgm /	8,00 mgm /	830 0 mgm /	444 0 mgm /	258 0 mgm /	
Free cholesterol	310.0	135 0	134 0	99 0	137 0	
Cholesterol present as esters	360.0	735 0	696.0	345.0	1 210 0	
Total phospholipids				1 000 0	1 880 0	
Cephalin						
Lecithin						
Total fatty acids						
Neutral fat fatty acids						
Neutral fat						
Bile acids	3.4					
Bilirubin (direct)	5 3					total
Bilirubin (indirect)	7 3					19 50

Patient on cholesterol free diet
† Fever due to tuberculosis

portal areas could be readily counted This afforded a fair and adequate interpretation of the underlying disease Preparations of this size removed without trauma or coagulation are so much better than fragments extracted by needle biopsy

Microscopic Findings in Biopsy Specimen—The pattern of the liver was well preserved and all portal areas lobules and central veins were easily identified The pathological change was centered in the perilobular or portal connective tissue This change involved all portal areas but the lesions varied in size No portal area in any of the sections could be con

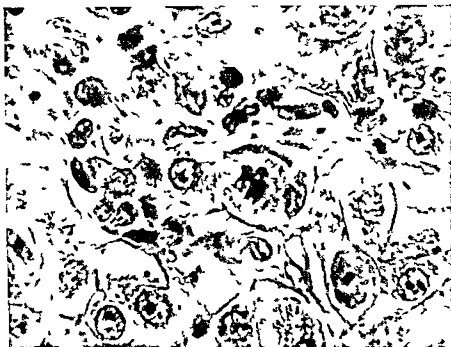


Fig 30 Liver from biopsy case XVI This field was selected to show a liver cell in mitosis The cell is swollen and larger than those bordering it The nuclear membrane is lost and the chromatin forms a coarse cluster in the center of the cell

sidered normal The lesion was characterized by a non specific subacute to chronic inflammatory reaction centered at the junction between portal area and lobule (Fig 7) It was characterized by a proliferation of fibroblasts the formation of new capillaries a light deposition of collagen and a variable infiltration of cells These included neutrophiles lymphocytes monocytes plasma cells eosinophiles and very rarely a multinucleated giant cell

TABLE VI

	Normal	11 , 37	1 1 40	6 1 40	2 7 41
Total cholesterol	150 60 mgm /	1,460.0 mgm /	1 140 0 mgm /	840 0 mgm /	1 040 0 mgm /
Free cholesterol	40 70	155.0	406 0	250.0	300 0
Cholesterol present as esters	,0 75 / of total cholesterol	1 305.0	734 0	590.0	740.0
Total phospholipids	150 50 mgm /	300 0		1 57 0	
Cephalin	10- 30	,0.0			
Lecithin	140 2 0	2 1 0 0			
Total fatty acids	200 450	1 9 0.0			
Neutral fat fatty acids	0 150	0			
Neutral fat	0-150	0			
Bile acids	0 2 '	5.0	8 0	6.44	
Bilirubin (direct)		6 60 "		3 6	
Bilirubin (indirect)		6 60		5.4	

	7 22 41*	11 14 41	1 7 42*	7 5 4	1 16 43†	27 3 death
Total cholesterol	6,0 0 mgm /	8,0 0 mgm /	830 0 mgm /	444 0 mgm /	258.0 mgm /	
Free cholesterol	,10.0	135 0	134.0	99 0	137 0	
Cholesterol present as esters	360.0	735.0	696.0 '	345 0	1 210 0	
Total phospholipids				1 000 0	1 880 0	
Cephalin						
Lecithin						
Total fatty acids						
Neutral fat fatty acids						
Neutral fat						
Bile acids	3.4					
Bilirubin (direct)	5 3					total
Bilirubin (indirect)	7 3 "					19 50

* Patient on cholesterol free diet
† Fever due to tuberculosis

of Disse In this manner liver cells singly and in cords become bordered by inflammatory granulation tissue (Fig 29) The sinus at first narrowed by this increase in fibroblasts later disappears At this stage the histological picture suggests a solid wedge of granulation tissue separating and compressing intact and broken cords of liver cells In the early stages the marginal liver cells remain unchanged but later when they become engulfed in fibrous tissue they show a series of regressive changes Some of them swell to twice their normal size and accumulate vacuoles in their

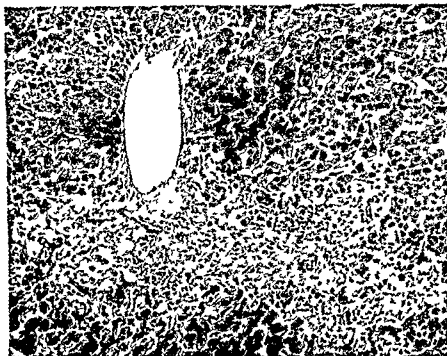


Fig 31 Liver from biopsy case XVI This field was selected to show the extension of an inflammatory process from the adjacent portal area out to the edge of a central vein The central vein itself is dilated and most of the surrounding lobule is free of pathological change

cytoplasm In some the cytoplasm becomes granular and eosinophilic Other liver cells accumulate bile and still others show necrosis and disintegration

Signs of liver cell regeneration were found in the peripheral zones of lobules (Fig 30) This was shown by the presence of mitotic figures The very few small bile ducts that were visible in the portal areas were so compressed and flattened that they resembled solid cords of endothelial cells There were no leucocytes or bile casts within the lumina of any of these

The small bile ducts so readily seen in the portal areas of healthy livers could not be identified. The lymphatics and terminal branches of the portal vein were compressed, narrowed and in areas obliterated by inflammatory granulation tissue (Fig. 28). The small arteries were unchanged. This inflammatory reaction originating in and radiating out from, the portal areas led to variable and often irregular expansion of the perilobular connective tissue. The picture suggested a spilling over of inflammatory tissue from the portal areas into the peripheral zones of the lobules. The lines of



Fig. 31. Liver from biopsy case XXI. This field was selected to show the junction of a central vein with a sublobular vein. The vessels are dilated and contain few cells. The endothelial cells lining the vessel are flat and inconspicuous. The surrounding liver cells are orderly and bear a normal relationship to sinus endothelium. There is no trace of inflammation. Fields of this sort were common and stood out in sharp contrast to the changes going on in the periphery of the lobule.

demarcation between portal connective tissue and lobules were poorly defined because of this infiltration of inflammatory granulation tissue into the bordering parenchyma.

In the beginning, the reaction is centered about the terminal bile ducts and is confined to the portal areas. From here it spreads into the most peripheral portion of the lobule by infiltrating along the perisinusoidal spaces

Rarely the inflammatory reaction in the portal area cut deeply into the lobule and in one field a continous track of granulation tissue could be traced from the portal area to the central vein (Fig 32) The type and extent of the cellular exudate warrant a more detailed description In some fields the cellular infiltration was minimal In other areas it so dominated the field that it obscured completely the underlying granulation tissue One field showed nests of polymorphonuclear leucocytes another was dominated by lymphocytes and histiocytes

To summarize the overall picture it may be said that the liver was the seat of an active subacute to chronic inflammatory reaction centered in the portal areas This was characterized by an increase in inflammatory granulation tissue with a corresponding widening and lengthening of the portal connective tissue There was a tendency for portal areas to unite and to form thin barriers of perilobular fibrosis There was bile stasis within the lobules and many of the sinuses were narrowed or blocked The nature of the reaction may be distinguished from the changes seen in obstructive and cholangitic biliary cirrhosis although its distribution is similar to that in both of these forms of cirrhosis Because the lesion is centered about the terminal bile ducts because it is characterized by an inflammatory process and particularly because at the present time the etiology remains obscure the histological designation Periocholangiolitic Biliary Cirrhosis is suggested

Autopsy Findings—The liver was large uniformly granular and bile stained On section the freshly cut surface showed a lobular but coarse pattern There was absolutely no suggestion of any type of extrahepatic biliary obstruction and no lipoid was seen in any part of the biliary tract

Microscopic Findings from Autopsy Specimen—The histology of the liver was now much more complex than in the biopsy taken fourteen months previously for now the pathology was much older and it was complicated by a very recent and terminal miliary form of tuberculosis

The pattern of the liver was badly distorted The portal areas were wide branching irregular and rich in fibrous tissue They reached out into the lobules and broke them into smaller and irregular nodules There were nodules of regenerated liver cells The liver parenchyma was edematous and delicate fibrous strands extended far along the sinuses into the lobules (Fig 33) Some of the sinuses were collapsed some were distended with blood some of the sinuses contained nests of endothelial cells laden with lipoid Many of the liver cells showed hyaline degeneration Lastly there were tubercles in many fields

The large size of the liver the diffuse and extensive fibrosis the intracellular bile stasis and the still active inflammatory reaction in the portal areas offered a very complex histological picture It is interesting to compare the liver now with the biopsy specimen studied months earlier Common to both is the bile stasis the hyaline degeneration of liver cells (Fig 34) and the

bile ducts The junction ducts or canals of Hering so difficult to see in a normal liver, were accentuated by the ingrowth of inflammatory granulation tissue

Bile stasis was a striking finding First there were large and small casts of inspissated bile in the canaliculi of collapsed and compressed cords of liver cells Secondly there were coarse clumps of bile in liver cells bordering the portal areas There was no bile retention within the central zones of the lobules This seemed paradoxical for this is the common site of bile retention in simple extrahepatic biliary obstruction

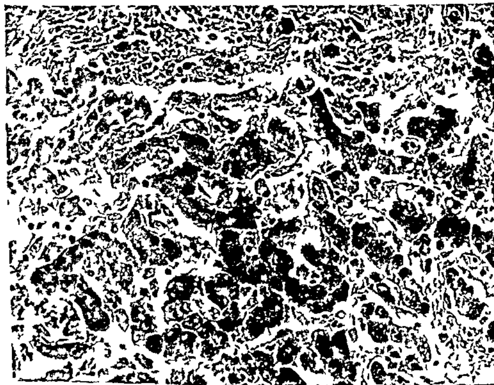


Fig 33 Liver from autopsy case XVI This field was selected o show a portion of the peripheral zone of a lobule or nodule of liver cells bordering an area of fibrosis The cords of liver cells are tortuous and widely separated The sinuses contain large lipoid laden histiocytes There is a moderate increase in perisinusoidal collagen The sinuses are collapsed and poorly defined

The sinuses adjacent to the portal areas were sometimes dilated and sometimes compressed The lining endothelial cells were for the most part inconspicuous but here and there an isolated endothelial cell was laden with lipoid The central veins and sublobular veins with few exceptions showed no sign of inflammatory granulation tissue (Fig 31)

values in the serum for total cholesterol (1 460 mgm per cent about 85 per cent present as esters) as well as for lecithin (2 120 mgm per cent, about 10 times those of normal) (5) The serum is transparent despite the high cholesterol and lecithin content Neutral fat is not present in measurable amounts

Thannhauser[10] suggested that the accumulation of cholesterols and lecithin in the serum at the outset of xanthomatous biliary cirrhosis should be caused by an increased formation of these substances in the liver by a functional disturbance of the liver cells Histological examination of this patient s liver had already revealed in the early stages fibrotic changes in and around the finest bile capillaries At this point it seems appropriate to consider which of three possibilities is concerned with the pathogenesis of the disease (1) Whether the assumption of an increased formation of cholesterol and lecithin in the liver is justified (2) Whether these substances are only retained in the serum by an impaired elimination due to fibrotic obliteration of the finest bile capillaries or (3) Whether both processes namely increased formation and retention cause the high values for cholesterol and lecithin in the serum The clinical and laboratory findings during almost three years of observation of this unique case provide the basis for such a discussion An increased formation of cholesterol and lecithin may be indicated by the following findings

1 The total cholesterol of the serum 1 460 mgm per cent on an unrestricted diet could not be reduced lower than about 800 mgm per cent cholesterol and 1 000 mgm per cent lecithin on a diet free of animal cholesterols and fats These high cholesterol and lecithin values were maintained during the period of diet treatment for two and a half years (see Table VI) This observation suggests that an excessive endogenous production of cholesterol and lecithin persisted while the exogenous quota of animal cholesterol supplied by food meanwhile was almost completely restricted

2 The cholesterol concentration in the serum decreased markedly and was almost normal in the final period of the disease because an inter current tuberculous disease with miliary dissemination in the liver caused the replacement of the liver parenchyma to a large extent The obliteration of the finest bile capillaries producing the retention continued dur ing this terminal phase but not enough functioning liver tissue remained to maintain the formerly increased cholesterol formation One may object to such an explanation referring to experiences where the total

widening of the portal areas In the biopsy specimen the lobular pattern was retained, at the time of autopsy there was little of the original pattern recognizable The large bile ducts at the hilus of the liver and radiating throughout the liver were collapsed and empty In none of the intrahepatic bile ducts were xanthoma cells demonstrable The classification of this type of cirrhosis when seen for the first time in its end stages at the autopsy table is difficult and often uncertain It is difficult to realize that a lesion that begins in the portal areas can lead to such destruction

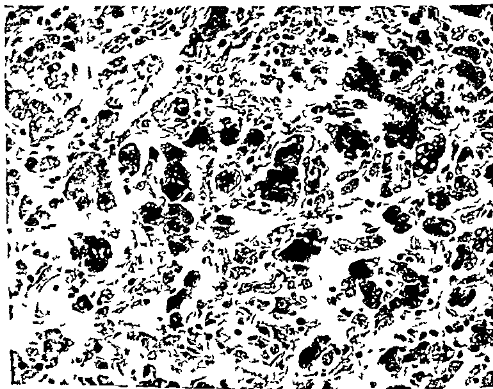


Fig 34 Liver from autopsy case XVI This field was selected to show a group of liver cells adjacent to a portal area containing large deposits of coarse eosin staining hyaline The cords of liver cells are broken up and sinuses are collapsed by perisinusoidal edema and fibrosis

Clinical Comment on Case XVI D L M — The patient exhibited during the first two years of observation the typical clinical characteristics of xanthomatous biliary cirrhosis as suggested by Thannhauser and Magendantz (1) Skin xanthoma (xanthelasma of eyelids tuberous xanthoma on elbows xanthoma of the creases of the palms) (2) Enlarged liver and spleen (3) Obstructive type of jaundice with bilirubin giving the direct and indirect van den Bergh reaction (4) Extremely high

cases the skin xanthoma disappeared as soon as the bile flow was restored while in xanthomatous biliary cirrhosis the skin xanthoma persist despite the fact that bile is constantly excreted in the intestines

The clinical and laboratory data collected during the period of observation favor the suggestion of Thannhauser[4 430] that the marked accumulation of cholesterol and lecithin at the beginning of xanthomatous biliary cirrhosis is probably not only the result of a retention of bile but rather the consequence of an imbalance of increased cholesterol and lecithin production and an inadequate excretion of these substances The explanation of the finding of excessively high cholesterol and lecithin as the result of hyperproduction of cholesterol and lecithin in xanthomatous biliary cirrhosis remains a hypothesis Such a hypothesis is however supported by the laboratory findings and by a comparison of this and other cases of xanthomatous biliary cirrhosis with other clinical syndromes where the obstruction and bile retention is complete and the only etiological factor In the cases of complete obstruction the lecithin and cholesterol content of the serum is by far not as high as in xanthomatous biliary cirrhosis despite the fact that in this disease the bile flow is always patent

Case XVII—T P 38 year old female of Finnish descent is married and has two children She was always well until she had menstrual disturbances in January 1938 when she was operated on for a fibroma After leaving the hospital in February she felt an itching all over her body One week later she had attacks of abdominal pain and noticed that her skin was jaundiced She did nothing until May 1938 when she saw a doctor for her jaundice which has never since then completely cleared Her appetite was good There were no chills or fever

First Admission to the Massachusetts General Hospital Boston * March 0 1940 Jaundiced patient with no complaints Heart normal in size no murmur Blood Pressure 108/79 Liver enlarged spleen not felt Laboratory findings bilirubin 6 9 biphasic reaction prothrombin time 9 1 (normal 21 0) Hinton reaction negative Discharged to the outpatient department with the diagnosis biliary cirrhosis and jaundice Transferred to the Surgical Department May 19 1940 Physical examination showed the same findings of an enlarged liver and chronic jaundice The patient was seen also at the dental clinic for dental bleeding Laboratory findings bromsulphthalein test 80 per cent rentention non protein nitrogen 18 mgm per cent total protein 7 1 gm per cent bilirubin van den Bergh 13 0 mgm biphasic

Exploratory Laparotomy—May 9 1940 (Dr A W Allen) No fluid

* The author is indebted to Dr J Howard Means and Dr Tracy B Mallory of the Massachusetts General Hospital for permission to use this case

cholesterol values are always very low in cases of hepatic failure, such as in acute yellow atrophy of the liver and in the last stages of a decompensated portal cirrhosis This patient however, never had hepatic failure nor hepatic coma but died as a result of tuberculosis of the lung and disseminated tuberculosis

3 The cholesterol and lecithin level in the serum in complete obstruction of the common bile duct resulting from occlusion by a stone, carcinoma or fibrosis after a surgical accident, is never as extremely high as in xanthomatous biliary cirrhosis, that is values as high as 1,450 mgm per cent total cholesterol and 2,120 mgm per cent lecithin observed in case XVI and in the first stages of other cases of xanthomatous biliary cirrhosis in this section The early liver biopsy on case XVI showed obliterative changes in the finest bile capillaries only in some areas of the liver It, therefore seems, unlikely that the fibrotic obliteration of some cholangioles in parts of the liver at the beginning of the disease should result in a much greater retention of cholesterol and lecithin than is observed in a case with complete occlusion of the common bile duct[109, 110] With regard to case XVI bile certainly was always produced and that a fair amount reached the intestines was demonstrated by the presense of urobilin and urobilinogen in the feces and urine during the course of the disease and by the aspiration of dye-stained bile from the patient's common duct during the operation As the disease progressed the fibrotic changes of the cholangioles involved greater areas of the periportal space Thus the retention of bile certainly was increased but the cholesterol and lecithin values in the serum decreased the more the liver parenchyma was replaced by fibrotic tissue It may also be noted that the bilirubin values in the serum at the outset were never outstandingly high and definitely not as elevated as those observed in complete blocking of the common duct The level of bilirubin in the serum of these patients does not parallel the increase or decrease of cholesterol and lecithin

4 Skin xanthoma were already developed in this case in the early stages of the disease (first year) at a time when the bilirubin was only moderately increased As far as can be ascertained from the history of the patients skin xanthoma did not precede the jaundice Patients with complete obstruction of the common bile duct by stone carcinoma or surgical obstruction exhibit a severe grade of jaundice a moderate increase of cholesterol and a slight increase of lecithin but skin xanthoma usually do not appear[101] The rare instances of skin xanthoma reported[103] after surgical obstruction seem rather exceptional In these

Third Hospital Admission March 1941 —Between January and March 1941 innumerable xanthoma developed on the patient's face arms elbows legs and feet (Fig 35) The creases of the palms showed many flat xanthomatous lesions firm and yellow linear and rounded in character X ray of the esophagus and stomach did not reveal esophageal varices Prothrombin time taken several times was normal Patient was now in the out patient department repeatedly The clinical picture did not change

Fourth Hospital Admission, May 1941 —The patient was hospitalized because of an acute cellulitis of the left leg After she recovered the author (Thannhauser) was allowed to see her through the courtesy of Dr James H Means and to examine the serum for the various lipids The skin especially around the neck was dark brownish The jaundice was of moderate grade Liver was four fingers below the costal margin The spleen was large and firm There was no ascites Plain xanthoma were noticed around the eye lids and in both creases of the hands The tuberous form of xanthoma firm and of a yellow carotene color appeared on her face neck elbows lower arms and legs Laboratory findings Van den Bergh 7 9 direct 9 6 indirect For lipid partition see Table XII

Fifth Hospital Admission April 1944 —Patient was admitted with bleeding from esophageal varices No history of alcohol intake During the past few months the patient had felt exhausted but did her housework About two weeks before her admission the stools became tarry The day before admission she had a peculiar sensation below the sternum and vomited a tablespoon of bright blood Her general appearance was the same as previously The liver and spleen were enlarged There was ascites Laboratory findings non protein nitrogen 35 mgm per cent bilirubin 6 6 direct 9 3 indirect total serum protein 5 3 gm per cent albumin 7 gm globulin 2 5 gm (April 5 1944) hemoglobin 3 5 gm red blood cells 1 500 000 white

TABLE XII

Lipid Analysis of the Serum of Patient T I (Case XXII)
The serum is transparent and not milky

	May 1 1941 Analysis at Research Laboratory Boston Dispensary	*April 5 1944 Analysis—Mass General Hospital*	*Normal*
Total cholesterol	1 115.2 mgm %	368.0 mgm %	150 60 mgm %
Free cholesterol	143.0 "		40- 70 "
Cholesterol per cent as esters	972.0 (87 of total cholesterol)	110 0 (29% of total cholesterol)	50 75 mgm of total cholesterol
Total phospholipids	2 40.0		150 60 mgm
Cephalin	50.0		
Lecithin	1 710.0	6 5.0 "	
Serum lipase	Normal		
Diastase	"		
Acid phosphatase			
Alkaline phosphatase	27 5 Bodansky units		

found in the abdomen Spleen was three times larger than normal Liver was moderately enlarged with surface not scarred or nodular but slightly greener than normal Head of the pancreas was normal, but the pancreas was thickened Bile duct was identified The common duct was probed No stones were found above and below or toward the gallbladder Dark bile could be seen coming from the gallbladder No stones were found Bile duct was roughly 7 mm in diameter Comment after careful exploration there was no evidence of stone in the duct or gallbladder

Liver biopsy (see under Pathology)



Fig 35 Case XVII Xanthelasma of both eyelids tuberous xanthoma of face and neck jaundice and yellow brownish pigmentation of face and neck Xanthomatous involvement of the creases of both hands

Second Hospital Admission —Patient had pain on her left side, no loss of weight Flank pain on both sides Jaundiced with yellow sclerae Bleeds from the gums very easily Some brown pigmentation on her face and abdomen Laboratory findings non protein nitrogen 29 mgm per cent total protein 5 8 gm per cent bilirubin 9 7 mgm per cent biopsy of skin showed no evidence of hemachromatosis

Patient was seen in the out patient department and was constantly jaundiced Bilirubin 8 5 biphasic prothrombin time 19 sodium 139 7 mgm per cent

litis with beginning pericholangiolitic biliary cirrhosis The diagnosis of the liver at the time of the autopsy was difficult and an accurate interpretation of the pathogenesis of this type of cirrhosis without the earlier biopsy would have been extremely hazardous

Clinical Comment —Patient T P Case XVII presented the following picture during the course of the disease (1) continuous jaundice (five years) ( ) skin xanthoma (plain and tuberous type for three years), (3) enlarged liver and spleen (4) extremely high total cholesterol as well as lecithin values in the serum (1 115 mgm per cent for cholesterol and 1 170 mgm per cent for lecithin (5) transparent serum despite the high cholesterol and lecithin content These clinical features correspond with those of xanthomatous biliary cirrhosis In the last phase of the patient s illness the values for total cholesterol as well as for lecithin decreased probably because of the progressing cirrhosis which also produced portal obstruction Varicose veins of the lower esophagus caused considerable bleeding and led to her death It is evident from the exploratory laparatomy and from the liver biopsy four years previously that the disease did not start with extensive changes in the liver parenchyma nor with obstruction of the common bile duct After an insidious onset jaundice of moderate grade was the first symptom lasting the entire five years of illness Skin xanthoma were noticed by the patient two years later The skin xanthoma persisted even in the final stages, although the cholesterol values of the serum decreased considerably because of the progressing cirrhosis It may however be noted that the concentration of cholesterol and lecithin in the serum remained higher than normal until the patient s death

Case XVIII —This 48 year old housewife Mrs P H was referred by Dr Edward S Medoff to the J H Pratt Diagnostic Hospital on April 7 1941 with skin trouble and jaundice as her chief complaint

Seven or eight years ago this woman first noticed the occurrence of dermatographia If she marked her skin with a match as in making initials the contacted area would become red and raised this would last for several minutes and disappear In the fall of 1937 she noticed the onset of weight loss and had a generalized inertia After doing moderate exercise she would feel all in and had no strength Weight loss of about two pounds a week continued When these symptoms first appeared she weighed approximately 134 pounds and within a period of several months she lost thirty to forty pounds

In January and February of 1938 she felt a generalized itching so marked and distressing that she visited a doctor in March The physician who had known her for a long time was quite surprised to see how yellow her skin

TABLE VIII

Analysis of Liver Tissue After Autopsy Dec 19 1944

		Normal / of dry weight
Total cholesterol	/	0 .6 /
Free cholesterol	1 07 /	0.44 0 55 /
Cholesterol present as esters	0 13 /	1 5 15 /
Total phospholipids	7 0	9 0 11 0 /
Cephalin	5 2 /	3.0 5 5 /
Lecithin	1 8 /	3.0 6.0 /
Total fatty acids	13 25 %	8 6 13.0 /

blood cells 1 00 polynuclears 84 per cent small lymphocytes 9 per cent, monocytes 0 eosinophiles 0 platelets decreased (April 1944) hemoglobin 49 per cent red blood cells 3 0 0 000 stool guaiac + + + +

Sixth Hospital Admission, Dec 16, 1944 —Patient had had esophageal bleeding General appearance unchanged Laboratory findings hemoglobin , 0 gm red blood cells 2 00 000 polynuclears 90 per cent lymphocytes 6 per cent monocytes per cent, urine specific gravity 1 106 albumin + bile + + + no tyrosine or leucine crystals were seen Patient died Dec 18 1944

Pathology —The biopsy specimen (permission to study the liver biopsy was obtained by Dr H L MacMahon through the courtesy of Dr Tracy B Mallory) from the liver of May 29 1940 of this patient showed a subacute to chronic inflammatory reaction in every portal area In addition there was severe bile stasis within the lobules The inflammatory reaction was confined to widened but well demarcated portal area Junction ducts were numerous but small bile ducts in contrast, were difficult to find Neither bile nor leucocytes were seen within any of the bile duct lumina Liver cells bordering the portal areas showed regressive changes No xanthoma cells were found in any of the portal areas

The histological findings from the liver at the time of autopsy December 18 1944 were quite different The uniform distribution of the early inflammatory lesion was replaced by a very patchy disorderly and far advanced perilobular fibrosis There was little cellular exudate, and in these wide communicating bands of fibrous tissue there were very few, small insignificant collapsed empty bile ducts In some areas whole lobules had been destroyed and in other areas the structure of the original lobules was little changed There was a diffuse and severe bile stasis most marked in distended canaliculi bordering zones of fibrosis An interesting finding was the accumulation in some of the dilated sinuses of endothelial cells containing lipoid but it must be emphasized that no xanthoma cells were found in any of the bile ducts Scattered throughout the liver and complicating this picture of fibrosis were small nodules of regenerated liver tissue Chemical analysis of the liver is shown in Table VIII

The diagnosis of the biopsy specimen was that of chronic pericholangio

litis with beginning pericholangiolitic biliary cirrhosis The diagnosis of the liver at the time of the autopsy was difficult and an accurate interpretation of the pathogenesis of this type of cirrhosis without the earlier biopsy would have been extremely hazardous

Clinical Comment —Patient T P Case XVII presented the following picture during the course of the disease (1) continuous jaundice (five years) ( ) skin xanthoma (plain and tuberous type for three years) (3) enlarged liver and spleen (4) extremely high total cholesterol as well as lecithin values in the serum (1 115 mgm per cent for cholesterol and 1 170 mgm per cent for lecithin (5) transparent serum despite the high cholesterol and lecithin content These clinical features correspond with those of xanthomatous biliary cirrhosis In the last phase of the patient s illness the values for total cholesterol as well as for lecithin decreased probably because of the progressing cirrhosis which also produced portal obstruction Varicose veins of the lower esophagus caused considerable bleeding and led to her death It is evident from the exploratory laparatomy and from the liver biopsy four years pre viously that the disease did not start with extensive changes in the liver parenchyma nor with obstruction of the common bile duct After an insidious onset jaundice of moderate grade was the first symptom lasting the entire five years of illness Skin xanthoma were noticed by the patient two years later The skin xanthoma persisted even in the final stages although the cholesterol values of the serum decreased considerably because of the progressing cirrhosis It may however be noted that the concentration of cholesterol and lecithin in the serum remained higher than normal until the patient s death

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In January and February of 1938 she felt a generalized itching so marked and distressing that she visited a doctor in March The physician who had known her for a long time was quite surprised to see how yellow her skin

was and told her she had jaundice A blood Wassermann test was negative She now had become quite nervous and irritable Since she received no relief from the physician s medication she saw another doctor (1938) At this time she noticed raised areas on the palmar surfaces of both hands Small nodules appeared in the crevices of the skin and at the flexion point of the fingers gradually involving the entire hand The hands were quite swollen and she was unable to clench her fist The raised areas were smooth white at the beginning but later turned yellow These persisted and about 1939 similar lesions became visible around the eyes and then seemed to spread everywhere These smooth raised yellowish orange lesions were observed around the nose and on the neck as far down as the collar bone They covered the elbows as well as the flexor surface of the forearm the anterior aspect of the knees the posterior aspect of the ankles the skin over the tendon Achilles the toes and the hands The rectum and the buttocks also showed these nodules For about two years, there had been no particular increase or change in their aspect However if the patient happened to scratch one of them severely it bled and exuded a yellowish fatty material for a short time

In addition to the variously scattered skin lesions there had also been no marked change in the past year or two in the loss of weight weakness nervousness and continuous jaundice On November 10th the patient had four teeth removed followed by profuse gum bleeding In December 1940 her physician did not advise a blood transfusion for the anemia incurred from the blood loss but gave her instead iron pills by mouth which according to the patient had rebuilt her blood

In the past four months her complexion had become much darker Within the last two months blister like lesions had developed over the face nose and legs Her weight was now 83 pounds in contrast to 91 pounds the previous year Her appetite remained good Sometimes she had considerable abdominal distension with eructations of gas but this had been noted for a number of years She had had no other pain or discoloration of the skin prior to her present illness Since the itching was now quite marked and the skin deeply pigmented she entered the hospital for further diagnostic studies

The patient s father had died at the age of 78 of a shock her mother at 7 of pneumonia Her mother had had sixteen pregnancies Two children were stillborn and other others died in infancy The patient has two brothers and three sisters living and well none of whom have exhibited any disease or skin discoloration like the patient No history of tuberculosis cancer diabetes cardiac or renal disease

She has been married twice the first time 27 years ago After eight years her husband was killed in an automobile accident They had one child a boy now 6 years old She married a second time seventeen years ago her present husband a sheet metal worker is living and well

The patient was born in New Hampshire Her work had always been of a domestic nature Habits have been good diet adequate As a result of her present illness the patient has been advised to decrease her fat intake but she still eats a little butter

General health has always been excellent The patient has had the usual childhood diseases with no past sequelae She stated that at the age of eight she is said to have had malaria and remembers having shaking chills then There have been no operations no serious injuries



Fig 36 Severe jaundice Plain xanthoma (xanthelasma) around both eyes Plain xanthoma in the supra clavicular fossae Tuberous xanthoma of the face and neck (case XVIII)

There have been no headaches Her teeth have been bad for a number of years, at least eight or ten Her gums bleed quite easily more noticeably so during the last few years Her vision has been good She has had no difficulty in hearing no earaches no glandular swelling of the neck no sub-

sternal pain no precordial distress In the winter time she has a cough Appetite has always been good Bowel movements have been fairly regular She takes a laxative occasionally In the past two years her stools have been of different colors at times black as tar or yellow and sometimes yellow streaked or brown She states that the stools are very greasy "as if you had thrown in a cup of grease In the past two weeks she has felt a slightly irritating area posterior to the rectum especially when sitting on a hard chair Patient has always drunk much water and voids extensively Since



Fig 37 Plain and tuberous xanthoma of both palms in addition to xanthomatous involvement of the creases (case XVIII)

the presence of the jaundice the color of the urine has been quite brown There have been no dysuria pyuria or pain simulating renal colic Until onset of the present illness her periods were quite regular but are no longer so The last period was one month ago and the previous one five months prior to that The amount of flow has been decreased during the past two years Sometimes she has clots but no dysmenorrhea For the past two

years she has had difficulty in kneeling that is pain in the knees on marked flexion She knows of no swelling of the painful joints There have been no manifestations of allergy During the past two to three years the patient has been trying to decrease the amount of her fat intake

Physical Examination—On admission temperature 98 6 pulse 80 respiration 20, weight 83½ pounds, height 5 feet, 4 inches The patient is a



Fig 38 Tuberous xanthoma of upper arm and elbows (case XVIII)

slight middle aged woman who appears much older than her years She is mentally alert and quite jolly The skin is deeply yellow and pigmented The pigmentation is much deeper over the chest and abdomen Another striking feature is the conspicuous skin xanthoma lesions (Figs 36 37 38 and 39) These lesions include extensive xanthelasmata which are quite smooth and yellow orange in color around the eyes involving the upper lids more extensively than the lower ones (Fig 36) Several single papillary lesions

of a slightly yellow hue are found on the face as well as the nostrils On the lateral aspect of the neck at the collar bone are two (bilateral) areas of smooth slightly raised, xanthomatous deposits (xanthoma plana) (Fig 36)



Fig 39 Tuberous xanthoma of the patellas and lower legs (case XVIII)

Similar xanthomatous lesions appear on each flexor aspect of the forearm. Along the elbow are raised tuberous lesions which are nodular and easily moved about (Fig 38) Extensive nodular xanthomatous lesions cover the

palmar surface of both hands (Fig 37) The inferior aspect of both breasts at the points of approximation to the thorax show a linear deposition of xanthomatous material On the anterior aspect of the knee are tuberous xanthomatous lesions (Fig 39) also similar ones between the toes and several on the dorsum of the feet Numerous tuberous xanthoma also occur on the knuckles of the hands the region of the heel and on the skin over the Achilles tendon Widely dispersed xanthomatous nodules are found over the buttocks and a band of xanthomatous tissue appears around the anal orifice There are also tiny single yellowish smooth areas over the back and discrete xanthomatous nodules over the entire body There is a marked icterus of the sclerae and the buccal membrane including the pharynx As already mentioned the skin is deeply jaundiced everywhere The hair on the head is plentiful but greying

Eyes show no undue prominence Pupils are of moderate size and round The left pupil is somewhat larger than the right but both react well to light and accommodation Extraocular movements are well carried out no nystagmus The fundi show the discs to be well outlined as are the retinal arteries and veins There is a suggestive yellowish tinge to the fundi No hemorrhages or exudates are noted In the right nares there is a projection but it cannot be said yet whether it arises from the septum or from the concha No bleeding points of the mucous membranes were observed

The tongue protrudes in the midline without a tremor is slightly coated and fairly well papillated Lower teeth are dirty and carious several upper ones have been removed The pharynx is icteric Tonsils are small There is no post nasal discharge The hearing is good no mastoid tenderness There is no tenderness over the maxillary sinuses No glandular enlargement in neck neither is there generalized glandular enlargement Thyroid is not enlarged Trachea is in midline The breasts are soft with no nodules no tenderness Expansion of lungs is good and equal on deep percussion Lungs resonant throughout On ausculation no rales are heard Breath sounds are vesicular

Heart is not enlarged left border dullness being 8 cm from the midline in the left interspace Heart sounds are loudest at the fourth interspace just lateral to the border of the sternum Heart rhythm is regular Blood pressure 160/80 in the right arm Radial pulse is regular and equal Abdomen is rather protuberant The patient states that her umbilicus is now somewhat firm this being unusual she also thinks that the configuration has changed in the past year or two In the left upper quadrant is a small mass which on palpation is found to be a firm spleen extending a hands breadth below the costal margin The liver is easily palpable firm non tender and extends one hands breadth below the costal margin in the mid-clavicular line No other masses are felt No tenderness

There is no cyanosis of the nail bed no ankle edema There is no pain

or limitation in movement of any of the joints except the knee joints Patient cannot flex the left shank on the thigh the angle of limitation being approximately 45 degrees No swelling no tenderness or increased heat in any of the joints The patient also cannot completely flex the fingers because of xanthomatous lesions Cranial nerves are intact There are no motor or sensory disturbances Reflexes are active and equal

Laboratory Data—Urine on admission was amber in color very slightly cloudy of alkaline reaction with specific gravity 1 009 a slight trace of albumin no sugar no urobilinin normal urobilinogen It showed a three plus reaction for bile Sediment showed 1-3 red cells per high power field less than one leucocyte per high power field, scattered epithelial cells many bacteria one small clump of pus was seen

Blood on admission showed 71 per cent hemoglobin 3 69 million red blood cells with color index of 0 96 White blood cell count was 9 400 with 15 per cent bands 60 per cent polymorphonuclears 2 per cent eosinophiles 3 per cent basophiles 16 per cent lymphocytes 4 per cent monocytes The blood smear showed some isocytosis platelets appeared normal Blood fragility test—control hemolysis began at 0 42, it was complete at 0 3-, the patient s hemolysis began at 0 40 and was complete at 0 4 Supernatent fluid of first tube was yellow due to bilirubin checked with serum in saline plus water gave the same color For analysis of the serum for lipids see Table IX Icteric index was 150 bilirubin direct 15 9 mgm per cent indirect 20 4 mgm per cent Fasting blood sugar was 100 mgm per cent The bromsulphthalein liver function test using 5 mgm per kilogram of body weight showed over 50 per cent retention in one half hour and 50 per cent retention in one hour Blood sedimentation rate was 18 mm in twenty minutes 66 mm in one hour and 11- mm in two hours by the Westergren method Hinton Wassermann and Kahn tests were negative Blood lipase 0 48 c c of 0 05 normal potassium hydroxid per 1 c c of serum (lower limit value for lipase in serum of normal individuals) Prothrombin time was 35 seconds normal control 25 -5 seconds

TABLE IX

Lipid Analysis of the Serum of Mrs I H

The serum was transparent and not milky

	April ? 1941	*May 29 1941*	*Normal*
Total cholesterol	1535 mgm /	1140 mgm /	150 60 mgm /
Free cholesterol	75	320	40 70
Cholesterol present as esters	1260 (82 / of total cholesterol)	910 (,9 / of total cholesterol)	70 75 / of total cholesterol

X ray Examinations Oral Graham Test—Fourteen hours after double oral dye no distinct gall bladder shadow which can be considered to repre

sent the gall bladder can be recognized in the right half of the abdomen There is also no shadow after a fatty meal In the presence of jaundice the lack of filling of the gall bladder cannot properly be evaluated as to the presence of gall bladder disease

Gastrointestinal —Smooth passage of barium through the esophagus Slight herniation of the stomach mucosa above the diaphragm Normal relief of the mucous membrane of the stomach regular curvatures The stomach is slightly displaced to the right by an enlarged spleen Nothing unusual in the upper loops of the small intestines

Diagnosis There is no x ray evidence of varices or any pathological lesion of the stomach duodenum and upper loops of the small intestines There is no x ray evidence of any bone changes in long bones and skull Both diaphragms are smooth in outline with clear angles The lung fields are free from infiltration The heart is normal in size and shape There is no x ray evidence of a pathological lesion of the chest

During the seven day stay in the hospital the patient had no particular complaints Request for a sternal puncture and peritoneoscopy as well as the gynecological examination was refused

Mrs P H was seen again as an ambulatory patient on May 9 1941 She complained only about the itching of the skin She claimed that she kept her diet free of animal cholesterol and fat She did her housework and even went out dancing several times Physical findings were unchanged since her hospital admission Liver and spleen were enlarged There had been no attacks of pain or fever no ascites no edema of the legs For analysis of serum lipids see Table IX Bilirubin direct 1 indirect 16

The patient was uncooperative and did not appear for another examination Dr E B Medoff Woonsocket R I reported that Mrs P H (Case XVIII) died in February 1943 a rather slow lingering death accompanied by numerous hemorrhages from the gums mouth rectum and frequent vomiting of blood Permission for an autopsy was denied

Clinical Comment —The patient Mrs P H (case XVIII) exhibited the most extensive involvement of the skin with xanthomatous lesions in the experience of the author Since she was uncooperative towards the end the clinical and laboratory follow up studies in the final two years are incomplete It is evident from the report of the attending physician that this patient s death was caused by bleeding from esophageal varices this condition was the outcome of the progressing cirrhosis which finally also resulted in portal obstruction It is noteworthy that at the height of her disease during the period of clinical observation the cholesterol esters were neither diminished nor were signs of portal congestion like esophageal varices present As in case XVII the symptoms of portal obstruction occurred in the last phases of her illness but these features

were not related to the primary pathogenesis of the disease In other words the histological demonstration of portal cirrhosis in the end stages of a case of xanthomatous biliary cirrhosis (pericholangiolitic biliary cirrhosis) should not be taken as a sign that skin xanthoma and chronic jaundice are complications of the common type of portal cirrhosis Rather the reverse sequence of events seems to occur For years the fibrotic changes are localized only in the finest ramifications of the bile capillaries and junction ducts producing the characteristic clinical picture of xanthomatous biliary cirrhosis In the last phases, however, symptoms of portal congestion develop and lead to the fatal outcome

Case XIX —A 46 year old married white female Mrs F B entered the Evans Memorial Hospital * Boston on August 19 1943 Her chief complaint was jaundice of sixteen months duration In childhood the patient had had scarlet fever and diphtheria Subsequently she had always been well until the onset of her present illness She had however always been thin her best weight having been 108 pounds There was no history of typhoid exposure to toxic chemicals or alcohol ingestion Except for mild and transient bouts of diarrhea there had been no specific gastrointestinal disturbances

In January 194 the patient began to feel weak and rundown but had no localized symptoms Her friends and physician told her that she was quite jaundiced Subsequently her stools became light her urine dark and her skin itchy a dragging sensation developed in the right upper quadrant

Since she obtained no relief from a low fat diet her physician sent her to the Pondville Hospital and told her she might have a 'growth On June 8 194 an exploratory laparotomy revealed no obstruction in the extra hepatic biliary tract A biopsy specimen of the liver was obtained (for its description see under *Pathology*) A retrograde cholangiogram made after the operation showed no evidence of biliary tract obstruction

Following her discharge from the Pondville Hospital the patient weighed 88 pounds Many excoriations developed on her skin in May 194 some of them becoming secondarily infected The excoriations bled easily and there were several episodes of epistaxis The jaundice remained about the same Anorexia was quite prominent but there were no other gastro intestinal symptoms

In March 1943 yellow plaques appeared on the margins of both upper lids Subsequently other plaques developed on the flexor folds of her hands and both arms as well as on the back neck shoulders and axillae

* The author is indebted to Dr Chester Keefer Dr Franz Ingelfinger and Dr Charles Branch of the Evans Memorial Hospital Boston Massachusetts to Dr Gerald C Leary Resident Pathologist of the Pondville Hospital Walpole Massachusetts and to Dr Warren C Hunter Pathologist University of Oregon Medical School for permission to use case history and anatomical material in this study

Since the patient failed to show any appreciable change and since the attending physician noted progressive enlargement of her liver she was admitted on July 3 1943 to the Evans Memorial Hospital for further study At the time of her first admission there the jaundice had already lasted for sixteen months The skin xanthoma had developed about nine months previously

Physical Examination on July 1, 194, revealed a well developed moderately emaciated woman appearing older than her stated age sitting in bed and scratching Skin sclerae and buccal membranes were icteric Numerous xanthomatous plaques *were observed in the axillae on the flexor surfaces* of the arms and hands on the posterior surfaces of the thorax and on the eyelids Several of these were excoriated The hair follicles over the extensor surfaces of the thighs showed papulopustular eruptions There were no petechiae no spider angiomata Pupils reacted normally There were marked dental caries with one bleeding fungating nodule 4 mm in diameter below the left lower canine tooth Thyroid was not enlarged Lungs were clear and resonant Heart was not enlarged rate 60 regular Blood pressure 150/62 no peripheral arteriosclerosis Liver was palpable four fingers below the right costal margin firm nodular and non tender Spleen was not palpable there was a slight tenderness in the right lower quadrant Rectal examination revealed no hemorrhoids Cervix uteri was in posterior position non tender Reflexes were hyperactive Weight 98 pounds

Laboratory Data—Hinton test was negative Urine — color dark brown to dark yellow specific gravity ranged from 1 017 to 1 0 7 bile test was 4+ on thirteen occasions urobilinogen was present frequently as high as 1 64 dilution sediment was negative Red blood count ranged from 4 5 to 2 85 million and hemoglobin from 13 to 10 grams Prothrombin time on two occasions was 90 9 per cent of normal and 100 per cent of normal respectively clotting time was 14 minutes and 30 seconds bleeding time was 3 minutes and 30 seconds clotting time repeated 15 minutes and bleeding time repeated prior to discharge 3 minutes and 15 seconds White blood cell count on admission was 9 500 with 70 per cent polynuclears 25 per cent lymphocytes 3 per cent monocytes and 2 per cent eosinophiles White blood count varied between 6 000 and the admission count with differentials essentially the same Non protein nitrogen in blood was 26 mgm per cent total protein on two occasions was 7 65 gm per cent and 6 26 gm per cent with albumin on two occasions 97 and 2 38 and globulin was 4 68 and 3 88 and albumin globulin ratio of 0 63 and 0 61 Icterus index was 75 90 80 80 80 60 75 83 and 90 Calcium was 8 mgm per cent phosphorus 3 96 mgm per cent Stools were brown formed and firm guaiac negative Stools were negative for pathological intestinal bacteria on culture Intravenous hippuric acid excreted 1 8 mgm in two hours (unable to void in one hour) Alkaline phosphatase was 3 King Armstrong

units Van den Bergh qualitative was direct positive, quantitative 5 3 mgm per cent For cholesterol figures see Table X Duodenal drainage showed A bile light yellow B bile light yellow no crystals or parasites white blood cells ++ in mucus Carotene and vitamin A in serum carotene o gamma per cent (normal 100 to 50 gamma per cent) vitamin A could not be read because of excess and abnormal lipid content Serum total lipid content (ether extraction) 3 96 gm per cent Lipid tolerance test (1 gram fat per kilogram by mouth) fasting 4 3 gm per cent 3 hours 4 43 grams per cent 5 hours 4 - gm per cent Serum lipase 0 644 c c NaOH (normal) *Serum showed no gross lipemia, being quite clear Chylomicrons were markedly reduced in number* Three days stool daily fat intake of 50 gm weight of stool wet 454 gm, dry 148 5 gm stool fat 49 6 gm 3 days All aline phosphatase repeated was -1 King Armstrong units Van den Bergh, immediate biphasic quantitative 6 75 mgm per cent of bilirubin

X ray Examination —Skull vault not remarkable no localized areas of erosion or hypertosis vessel markings normal in size and distribution, no abnormality of bone texture was noted sella turcica was normal in size and contour Pelvis no evidence of bone pathology There was a soft tissue mass at the pelvis probably due to distended bladder Femora poorly defined osteolytic areas at the distal end of each femur not typical of any particular disease X ray of the chest showed no pathological change, no evidence of active pulmonary pathology

Clinical Course —Patient spent thirty-six days in the hospital Temperature showed a constant wide swing although almost always within normal limits except for two to three times when it rose to 100° F Pulse was in conformity with temperature but averaged between 50 and 70 throughout the hospital course Fluid intake and output were not remarkable Patient was up and around during her stay, complaining only of intense itching on various occasions Calcium gluconate was administered 10 c c of 10 per cent solution with occasional relief from itching On admission the patient weighed 94 pounds and on discharge weighed approximately 93 pounds Blood pressure during course ranged about 1 0/74

The patient was placed on a low fat low cholesterol diet She was later given o gm of lecithin three times a day as well as vitamins A B complex and D One tablet of desoxycholic acid also was given three times a day The patient however was unable to take lecithin adequately

Follow up Notes —The patient was put on a diet containing 50 gm of fat with no animal fat allowed She was advised to eat as many proteins as possible She was given daily three tablets of vitamin B complex 45 000 units of vitamin A and 9 000 units of vitamin D and twice a week 1 mgm of vitamin K Through the kindness of Dr Dragstedt she was given at first twelve and subsequently fifteen capsules of lipocaic daily

The patient made some improvement on this regimen Her weight now

is 101 pound as compared to 93 pounds at the time of discharge and she feels much stronger On the other hand the size of her liver has not changed appreciably The skin xanthoma also are unchanged The laboratory studies show no clear cut improvement in the serum carotene vitamin A and bilirubin content

Second Hospital Admission—August 2 1944—Red blood cells 1 6 0 000 hemoglobin 6 gm white blood cells 15 0,0 differential count normal Hematocrit 11 per cent M C V 73 M C V 36 Clotting time was 4½ minutes bleeding time 5¼ minutes During the patient s hospital stay red cell counts improved to 3 7 0 000 with 11 0 gm hemoglobin Stool showed four plus guaiac from fifth to ninth day two plus on tenth day and one plus thereafter Total plasma protein was 5 5 gm per cent albumin 1 94 globulin 31 albumin globulin ratio 0 59 Cephalin flocculation test ++++ X ray for esophageal varices was negative

Third Hospital Admission—September 21 1944—Patient remained on a diet low in animal fat and containing vitamin B complex and vitamin K Jaundice has not increased or decreased although pruritus has been less marked Two weeks prior to her third admission she had an episode similar to the one which precipitated her second hospital admission weakness dizziness and passage of black stools Three hours prior to the present admission she had another spell of weakness with passing of tarry stools After transfusions she recovered but stools remained positive for six days

Laboratory Data—Red blood cells 2 980 000 hemoglobin 7 6 gm white blood cells 12 050 total plasma protein 4 3 gm per cent albumin 2 1 globulin 2 Patient was discharged with hemoglobin 1 9 gm white blood cells 7 800 cholesterol flocculation ++++ For cholesterol analysis see Table X

Fourth Hospital Admission—December 1 1944—On the day of admission the patient vomited several times Vomitus was of a coffee ground color Patient was confused and dyspneic Dyspnea disappeared when she lay down

Laboratory Data—Urine showed 3+ bile Hematocrit ranged from 14-35 per cent Hemoglobin ranged from 5 5 to 12 gm white blood cells from 6 900 to 6 700 with normal differential count non protein nitrogen 43 mgm per cent total protein 5 3 gm per cent albumin 55 globulin 91 albumin globulin ratio 1 1 cephalin flocculation 4+ stools 4 plus guaiac for five days (For cholesterols see Table X)

Fifth Hospital Admission—September 29 1946—One week prior to admission the patient passed dark blood from her rectum and felt debilitated one days before admission she also passed dark red blood from her rectum and vomited bright red blood She felt weak and developed a terrible thirst Temperature 98 6 F pulse 10 respiration 0 Skin was dusky green yellow hue Skin xanthoma had not changed from the time of her previous

units Van den Bergh qualitative was direct positive quantitative 5 23 mgm per cent For cholesterol figures see Table X Duodenal drainage showed A bile light yellow B bile light yellow no crystals or parasites white blood cells ++ in mucus Carotene and vitamin A in serum carotene [illegible]0 gamma per cent (normal 100 to [illegible]50 gamma per cent) vitamin A could not be read because of excess and abnormal lipid content Serum total lipid content (ether extraction) 3 96 gm per cent Lipid tolerance test (1 gram fat per kilogram by mouth) fasting 4 32 gm per cent 3 hours 4 43 grams per cent 5 hours 4 [illegible]2 gm per cent Serum lipase 0 644 c c NaOH (normal) *Serum showed no gross lipemia, being quite clear Chylomicrons were markedly reduced in number* Three days stool, daily fat intake of 50 gm weight of stool wet 454 gm, dry 148 5 gm stool fat 49 6 gm 3 days Alkaline phosphatase repeated was [illegible]1 King-Armstrong units Van den Bergh immediate biphasic quantitative 6 75 mgm per cent of bilirubin

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The patient was placed on a low fat low cholesterol diet She was later given [illegible]0 gm of lecithin three times a day as well as vitamins A B complex and D One tablet of desoxycholic acid also was given three times a day The patient however was unable to take lecithin adequately

Follow up Notes —The patient was put on a diet containing 50 gm of fat with no animal fat allowed She was advised to eat as many proteins as possible She was given daily three tablets of vitamin B complex 45 000 units of vitamin A and 9 000 units of vitamin D and twice a week 1 mgm of vitamin K Through the kindness of Dr Dragstedt she was given at first twelve and subsequently fifteen capsules of lipocaic daily

The patient made some improvement on this regimen Her weight now

is 101 pounds as compared to 93 pounds at the time of discharge and she feels much stronger. On the other hand the size of her liver has not changed appreciably. The skin xanthoma also are unchanged. The laboratory studies show no clear cut improvement in the serum carotene, vitamin A and bilirubin content.

Second Hospital Admission—August 2, 1944—Red blood cells 1,6 0,000, hemoglobin 6 gm, white blood cells 1,050, differential count normal. Hematocrit 11 per cent, MCV 73, MCV 36. Clotting time was 4½ minutes, bleeding time 5¼ minutes. During the patient's hospital stay red cell counts improved to 3,7 0,000 with 11.0 gm hemoglobin. Stool showed four plus guaiac from fifth to ninth day, two plus on tenth day and one plus thereafter. Total plasma protein was 5 5 gm per cent, albumin 1.94, globulin 3.31, albumin globulin ratio 0.59. Cephalin flocculation test ++++. X ray for esophageal varices was negative.

Third Hospital Admission—September 21, 1944—Patient remained on a diet low in animal fat and containing vitamin B complex and vitamin K. Jaundice has not increased *or decreased*, *although pruritus has been less* marked. Two weeks prior to her third admission she had an episode similar to the one which precipitated her second hospital admission: weakness, dizziness and passage of black stools. Three hours prior to the present admission she had another spell of weakness with passing of tarry stools. After transfusions she recovered, *but stools remained positive for six days*.

Laboratory Data—Red blood cells 980,000, hemoglobin 7.6 gm, white blood cells 1 050, total plasma protein 4.3 gm per cent, albumin 2.1, globulin. Patient was discharged with hemoglobin 1 .9 gm, white blood cells 7,800, cholesterol flocculation ++++. For cholesterol analysis see Table X.

Fourth Hospital Admission—December 12, 1944—On the day of admission the patient vomited several times. Vomitus was of a coffee ground color. Patient was confused and dyspneic. Dyspnea disappeared when she lay down.

Laboratory Data—Urine showed 3+ bile. Hematocrit ranged from 14–25 *per cent. Hemoglobin ranged from 5 , to 1 gm*, white blood cells from 6,900 to 6,700 with normal differential count, non protein nitrogen 43 mgm per cent, total protein 5 3 gm per cent, albumin 55, globulin 91, albumin globulin ratio 1 1, cephalin flocculation 4+, stools 4 plus guaiac for five days. (For cholesterols see Table X.)

Fifth Hospital Admission—September 29, 1946—One week prior to admission the patient passed dark blood from her rectum and felt debilitated; one days before admission she also passed dark red blood from her rectum and vomited bright red blood. She felt weak and developed a terrible thirst. Temperature 98.6 F, pulse 10 , respiration 0. Skin was dusky green yellow hue. *Skin xanthoma* had not changed from the time of her previous

admissions light colored plaques ranging from 2 mm to 3 cm in diameter Heart showed systolic murmur blood pressure 94/35

Laboratory Data—Urine bile 9 + Blood sedimentation rate 99 per cent, hemoglobin 4 9 after ten blood transfusions 11 5 g Prothrombin time 44 seconds (control o seconds) Total protein 3 98 gm per cent albumin 1 87 globulin 1 61 gm per cent Total protein increased finally to 6 5 gm per cent Non protein nitrogen 4 3 For cholesterol values see Table X

Sixth Hospital Admission—April 17, 1947—Since her discharge the patient has been followed by Dr F Ingelfinger in the Outpatient Department of the Evans Memorial Hospital For about six months she has had a warty horn like papilloma at the inner canthus of the right eye Four days prior to her admission following a minor trauma she bled profusely and

TABLE X

	7 13 43	7 25 43	8 19-43	8 5 43	8 2 44	9-21 44*
Total cholesterol	545 mgm /	00 mgm /	545 mgm /	500 mgm /	545 mgm /	375 mgm /
Cholesterol present as esters	2 0 (40 / of tot chol)	20 (0 / of tot chol)	0 (40 / of tot chol)	20 (30 / of tot chol)	200 " (36 / of tot chol)	00 " (53 / of tot chol)
Total bilirubin	5 2	6 7			7.8	1 5
Alkaline phosphatase	3U	1U			17	24
Total phospholipids						
Saponifiable lipids						
Total fatty acids						
Neutral fat						

	10-11 44	12 14 44	9- 9-46	10-3 46	4 17 47	5 2 7
Total cholesterol	00 mgm	500 mgm	310 mgm	6 mgm	00 mgm %	75 mgm /
Cholesterol present as esters	333 (47 / of tot chol)	3/9 (70 / of tot chol)	50 (78 of tot chol)	60 (75 / of tot chol)	95 (45 / of tot chol)	9 (33 / of tot chol)
Total bilirubin		28.6	11 5		43 1	
(direct)		12 3	4.08		18 6	
(indirect)		16 3	7.44		24 5	
Alkaline phosphatase		45				
Total phospholipids						290 mgm /
Saponifiable lipids						194
Total fatty acids						667
Neutral fat						387

* After bleeding

has continued to bleed intermittently despite ligation by her local physician The patient also has noticed occasional bleeding from the gums Itching was at times very intense She followed a fat free diet only moderately well

Temperature 98 6 F pulse 68 The patient was a small thin female who appeared chronically ill but in no acute distress Skin was of deep

brownish yellow color and contained numerous plain and tuberous xanthomas particularly about the upper trunk and arms Over the legs the lesions resembled a marked hyperkeratosis follicularis (eruptive papulopustular lesions) Mucous membranes of the mouth were a yellow brown color Chest was clear to percussion and auscultation Heart point of apical impulse was in the fifth interspace 7 cm from the midsternal line and except for a grade 3 blowing systolic murmur was otherwise not remarkable The liver edge was palpable below the level of the iliac crest and in the epigastrium The liver was smooth and not tender



Fig 40 Liver from biopsy specimen case XIX This field was selected to show a widened portal area that is the site of a chronic inflammatory reaction The exudate is dominated by lymphocytes and mononuclear cells The inflammatory reaction seems to spill over into the adjacent lobule Small bile ducts are inconspicuous

Laboratory Data—Urine showed 4+ bilirubin and numerous tyrosin crystals *Blood sedimentation rate 108 per hour hemoglobin 10 8 gm or* 36 per cent albumin 88 globulin 3 69 Prothrombin time 4 seconds (control 1 98 sec) Cephalin flocculation 4+ Thymol turbidity 36 For cholesterol and bilirubin see Table X

The lesion of the inner canthus of the eye was healed at the time of the patient s discharge The patient was advised to stay on a high protein high vitamin high carbohydrate but low fat diet Arrangements were made to have her receive injections of vitamin K twice a week

Pathology—A biopsy was done at the Pondville Hospital in June of 1942 Exploration revealed no extra hepatic biliary obstruction Permission to study a section of liver and lymph node prepared at the time of biopsy was obtained through the courtesy of Dr Gerald C Leary, resident pathologist at the Pondville Hospital

Microscopic Examination of Biopsy Specimen—This was an unusually satisfactory section and included approximately fifty lobules The section was well cut and beautifully stained There were four serial sections on the one slide affording an opportunity to follow a lesion from section to section



Fig 41 Liver from biopsy specimen case XIX This section was selected to show a portal area and the adjoining liver parenchyma There is a very rich cellular exudate throughout the interstitial tissue The granulation tissue almost hidden by this cellular exudate reaches out into the adjoining lobules Small bile ducts are empty and inconspicuous

The most striking change was a chronic inflammatory reaction in each portal area (Fig 40) There was a marked bile stasis within the lobules and this was concentrated in the central zones A third change was the focal accumulation of inflammatory cells in the nests within the lobules and a fourth change was a focal derangement of the trabecular pattern of liver cells within the lobule In addition to these there was degeneration and necrosis of liver cells singly and in small clusters but a very careful search

failed to reveal a single mitotic figure in either liver cell or bile duct The sinus endothelium was swollen Some of the sinuses were dilated others were compressed The central veins for the most part were intact and free of pathological change but occasionally a few lymphocytes were clustered in this area This was particularly true when a band of inflammatory granulation tissue extends deeply into the substance of a lobule

The oldest and most conspicuous change lay in the portal areas These zones of connective tissue were larger broader and in some places exerted an obvious compression effect on the adjacent liver parenchyma In this

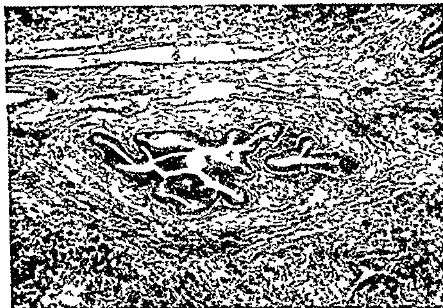


Fig 42 Liver from biopsy specimen case XIX This field was selected to show one of the larger bile ducts found in the biopsy specimen The lumen is empty and the epithelium is well preserved and hyperplastic The surrounding interstitial tissue is the seat of a chronic inflammatory reaction No bile and no leucocytes are visible within the lumen

biopsy specimen there were medium sized and terminal portal areas allowing an opportunity to study the inflammatory reaction about the small and larger vessels The inflammatory reaction was the same in the small and larger portal areas but it differed in extent from one area to another The reaction was confined to the interstitial tissue although there were changes in bile ducts veins lymphatics and arteries This reaction was dominated by a cellular infiltration and by a moderate proliferation of fibroblasts (Fig 41) Lymphocytes plasma cells and mononuclear cells were most numerous

In addition there were polymorphonuclear leucocytes and a slight scattering of eosinophiles In one field there was a very well formed lymph follicle There was nothing specific about the inflammatory reaction and there were no xanthoma cells The reaction although diffuse in the portal areas was associated most closely with the small and terminal bile ducts No leucocytes were found within these ducts The reaction extended to the outer margin of the portal area and spread in coarse and narrow extension into the peripheral zones of the lobules It blocked sinuses and isolated nests of liver cells

This extension into the lobule was confined to the outer zones of the lobule but occasionally where lobule and central vein were close it spread from one to the other Mitoses were found in histiocytes plasma cells and fibroblasts but no mitoses were found in bile ducts or liver cells

The bile ducts were of particular interest all large and small were empty The large were collapsed and the epithelium seemed hyperplastic and almost papillary (Fig 42) At no point was the epithelial lining of the larger ducts interrupted The medium sized ducts and the very small ducts were difficult to find Those that were visible were intact and empty Compressed liver cells and junction ducts which are composed of modified liver cells were very conspicuous They turned and twisted and lay embedded in inflammatory granulation tissue These compressed twisted and branching ducts suggested at first glance a great increase in small bile ducts The cells of the junction ducts often showed degeneration necrosis and leucocytic infiltration Some of these cells were deeply pigmented with bile These junction ducts appear to have suffered the greatest injury None of these cells showed fat vacuoles or hyaline degeneration

The intralobular bile canaliculi showed the changes of long standing biliary obstruction Casts were found throughout the lobules Some were obviously old and lamellated (Fig 43) There was a very definite intralobular bile stasis The greatest concentration of bile was in the center of the lobule and in the areas adjacent to these bile casts liver cells have undergone degeneration and necrosis

In summing up the findings in this case it seems important to point out that the inflammatory reaction was centered in the interstitial connective tissue and that changes within the lobules were secondary to this inflammatory reaction in the portal area Because of the location of the lesion it seems reasonable to consider it as a form of chronic pericholangiolitis and because there is already beginning cirrhosis the histological diagnosis of pericholangiolitic biliary cirrhosis seems acceptable

A section of lymph node taken at the time of biopsy showed three interesting changes (1) There was a hyperplasia swelling and accumulation of large mononuclear cells in dilated sinuses The cytoplasm of these cells was clear and vacuolated suggesting fat storage ( ) Many of the endothelial cells contained clumps of bile pigment This clearly showed the effects of

an intrahepatic bile stasis and the extravasation of bile from the liver into the lymphatics (3) There were areas of necrosis calcification and foreign body giant cells reaction A fourth finding although much less significant was a slight eosinophilia throughout the section In passing it is interesting to recall that all of these findings in the lymph node may be seen in lymph nodes in cases of simple uncomplicated extrahepatic bile stasis

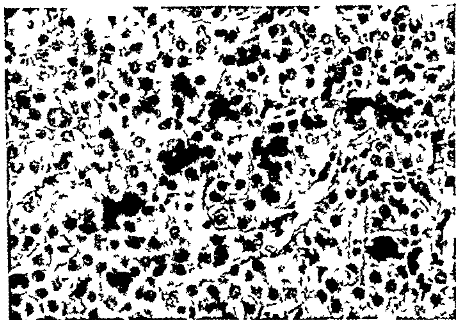


Fig 43 Liver from biopsy specimen case XIX This section was selected to show intralobular bile stasis *The bile canaliculi are distended with large deeply stained irregular and sometimes lamellated casts* Bordering liver cells show regressive changes and histiocytic infiltration

Clinical Comment —In addition to the numerous tuberous and plain xanthoma Mrs F B (case XIX) exhibited maculopustular lesions This type of eruptive lesion formerly described by Thannhauser and Magendantz is not as these authors believed pathognomonic for xanthomatous biliary cirrhosis since this author meanwhile has observed identical eruptions which appear and disappear intermittently and itch intensively in rare cases of chronic infectious hepatitis In contrast to xanthomatous biliary cirrhosis skin xanthoma never appear in chronic hepatitis notwithstanding the fact that in these cases cholesterol but not lecithin is moderately increased in the serum

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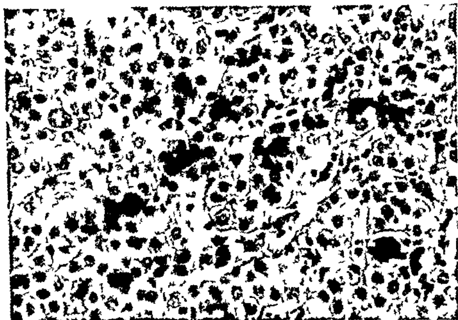


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Patient F B (case XIX) did not show comparatively high cholesterol values The cholesterols present as esters were already diminished one and one half years after the onset of the disease, other cases observed maintained a normal proportion of total cholesterol to cholesterol present as esters for a long time This case deviated from the pattern of cholesterol accumulation observed in other cases from this disorder The clinical features alone would not be sufficient to establish the clinical diagnosis of xanthomatous biliary cirrhosis beyond doubt if the histological findings in the biopsy at the beginning of the disease did not show pericholangiolitic biliary cirrhosis which is the underlying histological lesion of this clinical syndrome

Case XX —A 43 year old farmer s wife Mrs D C was admitted by Dr W C Burrage to the Joseph H Pratt Diagnostic Hospital on April 16 1947 In January of 1946 the patient visited her physician because of nose bleeds enlarged abdomen light colored fetid stools and much flatus Her doctor informed her that she was jaundiced and that her liver was enlarged He gave her bile salts and vitamins and also placed her on a high calorie high protein high carbohydrate fat free diet One month later she complained of pruritus She also experienced a pain in the right chest region with a fever of 104° F Sulfadiazine was prescribed and the temperature rapidly returned to normal The patient remained in bed for approximately six weeks and then was referred to a specialist in Halifax There her chest was x-rayed an upper gastrointestinal series was done and her stools and blood were examined Her hemoglobin was normal Her liver was still enlarged Everything else was normal The patient continued a fairly normal existence getting adequate rest and subsisting on the regimen outlined by her physician However she slowly and gradually went off the diet The pruritus became more intense The physician increased her bile salts

As no improvement was noted the patient was referred to Dr Burrage of Maine who recognized the nature of her disease and advised her to enter the Pratt Diagnostic Hospital The lesions on her body first noticed by the patient s sister on September 1 1946 had steadily increased in number Almost every crease of her body showed hard raised white nodules of varying sizes Nodular xanthoma were seen on the hands elbows eyes and both lower extremities as well as on the trunk and back Eruptive maculopustular lesions with a red base and a sunken in head were visible also on the extremities The true yellow xanthomata elsewhere over the body looked different and were not inflamed The hands have always been dry The pruritus continuous since February is possibly more intense The bile salts seem to darken the stools which are more brown than yellow The really light stools observed approximately one month ago seemed to occur with excessive fat indulgence The stools are bulky and well formed

and the odor is lessening She has never noticed black or bloody stools From the beginning of her illness the urine has been dark a dark amber color At times the smell is strong She seldom has nose bleeds at present nor bleeding from any of the orifices Occasionally her gums bleed after she brushes her teeth The patient menstruated last January one year ago at the onset of her present illness Her jaundice varies in intensity At times she is quite yellow other times she clear considerably but she is never completely free of it The patient lost her voice two weeks ago It began with a cold and her throat was irritated She has noticed a change in her voice since the fall of 1946 and cannot sing so well as previously

The patient's mother is living and well at the age of 73 Her father drowned at the age of 30 Three sisters are all well No family history of cancer tuberculosis kidney disease heart disease hypertension nervous disease convulsions or diabetes No family history of similar lesions or allergy

The patient had the usual childhood diseases She had scarlet fever when she was approximately 10 years of age There have been no major operations or serious illnesses

There have been no headaches vertigo syncope blurring diplopia scotomata tinnitus or otorrhea epistaxis has been mentioned There has been no dysphagia no cough no chest pain The patient perspires profusely and believes that she may have had hot flashes There have been no hemoptysis ankle edema shortness of breath or palpitation Her appetite is enormous she states that she can not get enough to eat Her weight has been stationary She has had no nausea vomiting or constipation Since the onset of her present illness she has had more frequent bowel movements now numbering two to four a day in contrast to the two bowel movements formerly Previously there had been nocturia once There is no burning dysuria or hematuria

Habits —The patient does not smoke or drink At the present time she is subsisting on a high calorie high protein high carbohydrate low fat diet She takes bile salts iron and vitamins She has also been given biotol and amino acid preparations

The patient was born in New Brunswick Canada and came to this country at 18 years of age She trained as a nurse at the Poughkeepsie Hospital She married at the age of 37 Her husband is seven years her senior They have two children Her husband and children are well

Physical Examination April 1947 —Temperature 99.4 F pulse 8 *respiration 18 height 5 3 weight 127½ pounds Blood pressure is 120/70* in the recumbent position The patient is a well developed middle aged woman in no acute physical distress She is pleasant cooperative and intelligent She speaks in a whisper because she is hoarse The skin is dark brown and peppered with xanthoma which are elevated yellow and hard and

which vary considerably in size Xanthoma are present practically all over the body the neck the chest the back arms hands and lower extremities There are also maculopapular lesions on the lower extremities which are different from the yellow xanthoma There is a cracking about the creases of the hands which are hard and dry and practically covered with xanthoma Hard yellow elevated nodular lesions also appear over the dorsum of the hands and seem to be localized over the joints Both elbow regions are involved and lesions are found in the antecubital fossae and over the extensor joint surface Both axillae exhibit white smooth hard lesions The back is peppered with lesions numerous areas of dark pigmentation unassociated with whitish discoloration at the present There is a chamois like color to the skin around both eyes The face is symmetrical There is no sinus and no mastoid tenderness No exostoses are present The auditory acuity is good The tympanic membranes are intact The pupils are round and equal react briskly to light and accommodation The extra ocular movements are in full range There is no nystagmus blepharitis conjunctivitis exophthalmos or enophthalmos The opthalmoscopic examination reveals well defined discs with no retinal lesions hemorrhages or exudates Nose no septal deflection rhinitis perforation or polyps Oral cavity shows no cheilosis The teeth are in good repair The tongue is not coated and projects in the midline the papillae are prominent no stomatitis gingivitis glossitis or pharyngitis There are no lesions similar to those observed over the body The patient has been hoarse for three months The vocal cords are thickened no definite xanthoma could be seen on the infiltrated cords Neck shows no rigidity tracheal deviation thyroid enlargement or cervical adenopathy The chest is symmetrical The breasts are small free of masses with no erosion of the nipples The lungs except for the right base which showed some rales are clear to auscultation and percussion The diaphragmatic excursions are good The heart is normal in size and position the rate is normal the rhythm regular There is a grade I to II systolic murmur heard over the entire precordium The abdomen is distended and asymmetrical There seems to be a definite fullness in the right side of the abdomen with bulging in the right flank On palpation one can feel a tremendously enlarged smooth liver that fills the entire abdomen except for the left flank The spleen can be definitely felt and palpated two fingers below the costal margin There is no fluid in the abdomen no shifting dullness There is no inguinal hernia no adenopathy The extremities are symmetrical The lesions present over both lower extremities have been mentioned There is no peripheral edema The dorsalis pedis pulsations are goods The spine exhibits the normal curvatures No tenderness elicited on percussion along the spine The joints are all freely movable The muscle strength and tone are good there is no atrophy paralysis fibrillation or tremor Coordination tests are well performed Sensations are intact

Reflexes are active and equal bilaterally No pathological reflexes were elicited Pelvic examination shows normal external genitalia There is a grade III to IV cystocele and marital introitus The cervix is in normal position There is a polyp protruding from the cervical os The uterus and adnexa were not pathological Rectal examination shows sphincter tone good no hemorrhoids no masses were outlined The stool was brown

Laboratory Data—Urine reaction alkaline sugar 0 albumin 0 specific gravity 1 0 3 some red and white cells visible in each field with high magnification rare squamous epithelial cells and very rare mucous threads bile reaction + urobilin reaction ++++ urobilinogen according to Wallace and Diamond positive 1 80 in dilution Blood hemoglobin 74 per cent 11 6 gm red blood cells 3 57 millions with color index 1 0 , white blood cells 9,450 polynuclears 69 per cent, bands 5 per cent lymphocytes 0 per cent monocytes 6 per cent Smear shows occasional target cell few macrocytes rare polychromatophilia no rouleaux Platelets normal in number Blood chemistry fasting blood sugar 87 mgm per cent total serum proteins 8 0 gm per cent albumin 3 7 globulin 4 3 Total bilirubin 9 0 mgm per cent direct 7 1 indirect 9 1 Blood sedimentation rate 20 minutes 28 1 hour 81 prothrombin time 26 seconds (control 24 seconds) For lipid findings in serum see Table XI

TABLE XI

Lipid Findings in Serum of Case XX

	April 14 1947	*April 17 1947*	*June 2, 1947*	*Sept 15 1947*
Serum appearance	yellow green clear	yellow green clear	yellow green clear	
Cholesterol—total	9 0 mgm %	962 mgm %	850 mgm %	616 mgm %
—free	830	915 "	750 "	448 "
—esters	90 (9.8 % of tot chol)	47 (4.9 % of tot chol)	100 (11 8 % of tot chol)	168 (2 % of tot chol)
Phospholipid total	1 750 mgm %	1 325 mgm %	1 750 mgm %	
Saponifiable lipids lecithin and cephalin		1,071	1,200	
Total fatty acids	1 540 "	1 180	1 700	
Neutral fat	35 "	30	0 "	
Bilirubin total	9		6 9	
Total protein	8 "			
Albumin	3 7 "			
Globulin	4 3			

Pathology—The specimens consisted of two small fragments of the liver tissue each approximately 0 4 × 0 3 × 0 2 cm On each there was a small but smooth area of capsular surface The tissue was heavily bile stained finely nodular and firm It cut with resistance and each had a coarse texture

Microscopic Examination of biopsy Specimen—Five sections were studied immediately on this viable fresh unfrozen and unfixed tissue Each showed

a lengthening and widening of the portal areas with an increase in interstitial fibrous tissue and a very rich lymphocytic infiltration The central veins and lobular pattern for the most part were well preserved By elongation and fusion with one another the enlarged portal areas had already formed a well advanced perilobular form of cirrhosis No bile was seen in these widened portal areas This stood out in marked contrast to the extreme degree of bile retention within the lobules All sections were studied with a polarizing microscope and all failed to reveal any double refractile fat No xanthoma cells were found in any part of the sections The portal veins and

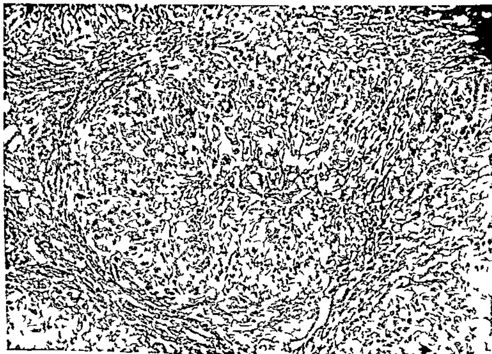


FIG 44 Liver from biopsy specimen stained for reticulum (case XX) A solitary lobule occupies almost the entire field with the central vein in the middle There is no increase of reticulum within the lobule although it is slightly concentrated in the central zone In the peripheral zone there is not only a condensation but an actual increase radiating out from the portal area

arteries in the portal areas were inconspicuous The terminal bile ducts were difficult to find There was no bile within any of the terminal bile ducts While the portal areas and lobules were clearly demarcated from one another it was possible to trace delicate icicle-like projections of fibrous tissue from the portal areas out between the liver cells of the peripheral zones of many of the lobules A rapid section diagnosis made at the moment of the biopsy was that of chronic pericholangiolitis with beginning pericholangiolotic

biliary cirrhosis There was no evidence of tumor or signs of extrahepatic biliary obstruction and there was no evidence of an active cholangitis The degree of liver cell degeneration was very limited

Later when the paraffin sections were ready a very careful histological study confirmed the earlier diagnosis Many of the lobules were well preserved and many of the central veins remained unchanged in the centers of the lobules (Fig 44) but in other areas central veins lay in immediate contact with widened portal areas (Fig 45) There was considerable loss of



Fig 45 Liver from biopsy specimen (case XX) showing an intact lobule with central vein clearly visible. The trabecular pattern is somewhat distorted and compressed and many small liver cells are mixed with those of normal size A zone of inflammatory granulation tissue encircles the periphery of the lobule

liver cells from the peripheral zones of the lobules The most striking finding was the presence of an unusually active chronic proliferative inflammatory reaction in the interstitial tissue of the portal areas There were many polymorphonuclear leucocytes throughout the inflammatory granulation tissue The junction ducts were increased and numerous They lay embedded in inflammatory granulation tissue They branched twisted and turned but could be readily followed from the lobules into the granulation tissue of the portal areas There were very few recognizable terminal bile

ducts or cholangioles In the paraffin sections bile casts were numerous in bile canaliculi and in dilated junction ducts but no casts were visible in the terminal bile ducts The inflammatory infiltration extended well out between the liver cells in the peripheral zones of the lobules and in this area the liver cells showed degeneration and necrosis

The overall picture was one of a very active chronic interstitial hepatitis centered about the terminal bile ducts and junction ducts at the outer margins of the lobules There was an increase in fibrous tissue a widening and fusion of the portal areas and a well advanced perilobular fibrosis No



Fig 46 Liver from biopsy specimen (case XX) A small nodule of compressed liver cells and sinuses There is no central vein This nodule of liver tissue is completely encircled by a widening zone of inflammatory granulation tissue radiating out from the peripheral zones of the lobule

xanthoma cells were found in any of the portal areas The final diagnosis was one of chronic pericholangiolitic biliary cirrhosis

This case shows the greatest destruction of liver tissue of any of the early biopsies and in some areas it is possible to find fields that are indistinguishable from those seen in subacute and chronic cases of infectious hepatitis (Figs 46 47 and 48) The complete picture however was distinctly one of an inflammatory reaction concentrated in the portal areas

Clinical Comment—Mrs C (case XX) exhibited most extensive

xanthomatous lesions of the skin, especially of the plain variety. Conspicuous not only on both eyelids and on the creases of the palm, these plain lesions developed in almost every place where the cutis is rather loosely attached to the subcutaneous tissues and wrinkles in longitudinal folds, such as around the neck, in the axilla and on the folds of the buttocks. The patient also had itchy maculopustular eruptions on the trunk and especially on both legs. It should again be emphasized that these maculopapular lesions are not the result of scratching.

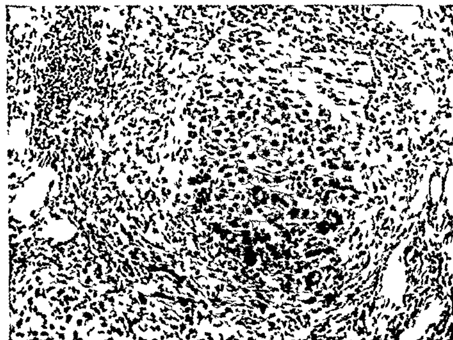


Fig. 47. Liver from biopsy specimen (case XX). This field was selected to show all that remains of a lobule of liver cells. There is an active inflammatory reaction at the periphery and extending along the sinuses between the liver cells. This was an unusual finding, but its resemblance to pictures seen in infectious hepatitis is at once obvious.

The patient's liver was extremely large and almost filled the whole abdomen, while the spleen extended only about one inch below the left costal margin. The liver, visible while a laparotomy for the biopsy was performed, revealed a fine granular surface with longitudinal scarring. Its color was reddish brown. Ascites was not present in the abdominal cavity.

The analysis of the serum lipids showed high values for lecithin (1 071 mgm per cent) and total cholesterol (962 mgm per cent) but only 5 per cent of the total cholesterol was present as esters These findings may be interpreted as significant of the severe damage of liver parenchyma In this case, in contrast to other instances of acute damage of liver parenchyma, such as in acute yellow atrophy of the liver or in fulminant cases of acute infectious hepatitis, the drop in cholesterol-

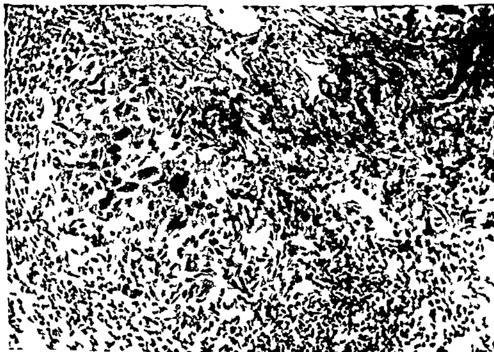


Fig 48 Liver from biopsy specimen (case XX) This field was selected and it is the only one of its kind in the entire section to show how completely a lobule may be destroyed in this expanding zone of inflammatory granulation tissue In the center of the field there are few moderately well preserved liver cells compressed together by this margin of granulation tissue This particular field shows perhaps the most striking lesion in the biopsy yet it is only fair to say that it was found only after long search and is not representative of the rest of the biopsy All transition between this lesion and the inflammatory reaction in the portal areas could be identified

esters (Estersturz)[43] did not occur together with low cholesterols but on the contrary with very high cholesterols in the serum This remarkable phenomenon may signify that an increased cholesterol formation is uninhibited in xanthomatous biliary cirrhosis even if an intercurrent parenchymatous damage impairs the esterification of cholesterols It is

unlikely that retention alone causes this phenomenon of very high cholesterol and very low esters The increased formation of cholesterol is, however lessened when in the course of the disease the liver parenchyma is replaced by fibrotic tissue as seen in Case XVI and Case XVII

Case XXa Mrs B F—The clinical diagnosis of xanthomatous biliary cirrhosis is usually suspected when skin xanthoma are found simultaneously with a large liver and spleen Recently however a jaundiced female 49 years with hepatosplenomegaly was observed who had no skin xanthoma but the analysis of her serum suggested the diagnosis of xanthomatous biliary cirrhosis We are indebted to Dr F Firestone of San Francisco for sending the patient to us for observation The sickness began with a chilly feeling on December , 1948 Jaundice was observed one month later

First serum analysis February 6 1949 San Francisco total serum bilirubin 3 8 total protein 7 61 albumin 3 6 globulin 4 03 thymol turbidity ++++ *Second serum analysis*, March 8 1949 1 71 total cholesterol 597 cholesterol esters (5 per cent of total) April 1949 total cholesterol 1860 and 1880 mgm per cent The stools were always colored Icteric index 40 to 68 *Serum analysis in Boston* May 17 1949 total cholesterol 1750 mgm per cent cholesterol esters 11 per cent of total total phospholipid 3 70 total fatty acids 1047 neutral fat 639 mgm per cent Cephalin flocculation ++ thymol turbidity ++++ total bilirubin 8 0 direct 6 3 indirect 1 7 Phosphatase 0 Bodansky units Bromsulphthalein 6 per cent in 1 hour

Liver biopsy after small abdominal incision (Dr Stuart Welch) normal color and smooth surface of the liver Histological diagnosis pericholangiolitic cirrhosis as found in early biopsies of cases of xanthomatous biliary cirrhosis (see Case XVI Fig 7 Case XIX Figs 40 41)

It will be of interest to see when and whether skin xanthoma will appear in this patient

Clinical Course

The onset is insidious The patients complain of an itching skin shortly followed by jaundice of the obstructive type i e bilirubin giving the direct and indirect van den Bergh reaction in the serum The jaundice continues up to the patient s fatal end with little variation in grade and seems rather independent of the development of skin xanthoma and the fluctuation of the cholesterol and lecithin values in the serum Fever or chills are not a feature of this disorder The development of a fever is the sign of an intercurrent complication (see Case XVI) The absence of fever probably explains why the patients feel relatively well during the course of the disease and are able to do their

housework The skin xanthoma appear many months after the jaundice Tuberous, deep yellow xanthoma are observed on the face, elbows, arms, fingers, buttocks and the distal parts of the lower extremities Plain xanthoma are found on the eyelids, the creases of the hand and in rare instances, in places where the skin is loosely attached to the underlying tissue forming folds as in the axillary folds and in the folds of the skin of the buttocks The localization of the skin xanthoma is different from that in the so called "disseminata" type of xanthoma characteristic of eosinophilic xanthomatous granuloma (normocholesteremic xanthomatosis, Schuller Christian's disease lipid granulomatosis) In this entirely different disease the xanthoma which are light yellow or deep sepia brown, are disseminated around the neck and trunk and arranged in linear clusters in the axilla The skin xanthoma in xanthomatous biliary cirrhosis persist throughout the disease The liver and spleen also remain enlarged In some cases (case XX) the liver extends in the midline below the umbilicus in others it is only moderately enlarged The surface of the liver is very firm but not nodular The color as seen in early exploration, is brownish red or green and the surface is smooth or slightly granular Later stages may show longitudinal scarring and larger granulation of the surface Ascites is not a feature of the disease Sometimes a peculiar intermittent maculopustular eruption appears all over the body and especially on the trunk and legs First inspection gives the impression that these lesions are only the result of scratching, but closer observation shows the sunken in head of the lesion mostly covered by a small crust The eruption is inflammatory in nature and does not contain foam cells Since similar eruptions occur in rare cases of chronic infectious hepatitis with chronic jaundice and moderately elevated cholesterols in the serum this type of maculopustular eruption even if seen most frequently in xanthomatous biliary cirrhosis is not an exclusive feature of this disorder

The analysis of the lipids of the serum provides the most decisive findings for the diagnosis of xanthomatous biliary cirrhosis The serum is transparent and not creamy during all stages of the disease It contains normal or small amounts of neutral fat despite its enormously increased content of cholesterols and lecithin At the beginning of the total cholesterol values of the serum may surpass 1 500 mgm per cent The cholesterol present as esters in the first year is normal or even abnormally high i e 70 75 per cent of the total cholesterol The percentage of the esters may even be higher than these normal figures In later phases the values for total cholesterol decrease but remain high Also the per

centage of the cholesterol present as esters becomes lower and the free cholesterol is more prominent The high values for lecithin decrease slowly with those for total cholesterol but they are found high even in the last stages of the disease A tendency towards bleeding mostly observed in chronic jaundice may occur The prothrombin time in the first years is mostly normal In the final phase however there is bleeding from the gums and mouth as a result of congestion Most of the patients die because of profuse hemorrhages from esophageal varices Portal congestion develops very late in this disorder X ray pictures of the esophagus during the development and height of the disease do not show esophageal varices nor are there other signs of portal congestion like ascites or spider veins Hepatic insufficiency resulting in hepatic coma was not observed in our cases Liver function tests are not of great value for the diagnosis of xanthomatous biliary cirrhosis since the clinical symptomatology is typical in all cases namely (1) skin xanthoma of the *plain and tuberous variety ( ) enlarged liver and spleen (3) obstructive* type of jaundice of years duration (4) extremely high values for total cholesterol as well as for lecithin (5) the serum is transparent and not milky because of its normal or rather low content of neutral fat

Clinical Features

Age and Sex —The patients in this group of xanthomatous biliary cirrosis are between 30 and 50 years of age except for a 7 year old girl described by Freda K Herbert[191] Female patients only have been reported so far[8 128 1 1 18 1 4 47] with the exception of Moxon s case[300]

With regard to male patients who have been observed with hepatosplenomegaly slight jaundice melanotic pigmentation of the skin increased total cholesterol and lecithin and skin xanthoma the question arises as to whether they should be classified in this group A Cantarow and C J Bucher[9] in a paper entitled *hemochromatosis described* a 45 year old man who exhibited a large liver and spleen together with xanthoma on both eyelids the creases of the palms and the flexor and extensor surfaces of the elbows There was also a blue bronze pigmentation and slight jaundice but no glycosuria Total cholesterol was 275 to 490 mgm per cent cholesterol present as esters 114 to 333 mgm per cent free cholesterol 33 to 157 mgm per cent The autopsy of the patient revealed hemochromatosis of the liver most extensively in the pancreas and lymph nodes

housework The skin xanthoma appear many months after the jaundice Tuberous, deep yellow xanthoma are observed on the face, elbows, arms, fingers, buttocks and the distal parts of the lower extremities Plain xanthoma are found on the eyelids, the creases of the hand and in rare instances, in places where the skin is loosely attached to the underlying tissue forming folds as in the axillary folds and in the folds of the skin of the buttocks The localization of the skin xanthoma is different from that in the so-called "disseminata" type of xanthoma characteristic of eosinophilic xanthomatous granuloma (normocholesteremic xanthomatosis, Schuller Christian's disease, lipid granulomatosis) In this entirely different disease the xanthoma which are light yellow or deep sepia brown are disseminated around the neck and trunk and arranged in linear clusters in the axilla The skin xanthoma in xanthomatous biliary cirrhosis persist throughout the disease The liver and spleen also remain enlarged In some cases (case XX) the liver extends in the midline below the umbilicus, in others it is only moderately enlarged The surface of the liver is very firm but not nodular The color as seen in early exploration, is brownish red or green and the surface is smooth or slightly granular Later stages may show longitudinal scarring and larger granulation of the surface Ascites is not a feature of the disease Sometimes a peculiar intermittent maculopustular eruption appears all over the body and especially on the trunk and legs First inspection gives the impression that these lesions are only the result of scratching, but closer observation shows the sunken in head of the lesion mostly covered by a small crust The eruption is inflammatory in nature and does not contain foam cells Since similar eruptions occur in rare cases of chronic infectious hepatitis with chronic jaundice and moderately elevated cholesterols in the serum this type of maculopulstular eruption even if seen most frequently in xanthomatous biliary cirrhosis is not an exclusive feature of this disorder

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it must be assumed that this syndrome with its typical features is so far confined only to females

Heredity—In none of the cases reported was a familial occurrence revealed by the history The group of familial hypercholesteremic xanthomatosis characterized by tuberous and plain xanthoma of the skin tendon xanthoma and atheroma formation on the inner lining of the arteries is a disorder which runs in families[113 10 4 1 4 450] Thannhauser and Magendantz[1 1 4 7] formerly believed that xanthomatous biliary cirrhosis also belonged to this group This opinion can no longer be maintained since in the meantime no familial incidence of xanthomatous biliary cirrhosis has been found It is now apparent that xanthomatous biliary cirrhosis is a clinical entity by itself

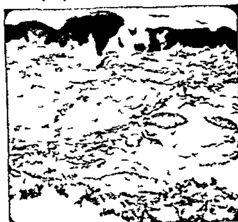


Fig 49 Histological picture of the eruptive (papulopustular) form of skin eruption Notice that no xanthoma cells are seen but there are defects of the skin and inflammation of the subcutaneous tissue

Skin—Tuberous and plain xanthoma are seen on the flexor surfaces as well as on the face and trunk In contrast to xanthoma disseminata they are always of an orange carotene like hue Xanthoma planum appears as plain xanthelasma on the creases of the palms and fingers The skin xanthoma in xanthomatous biliary cirrhosis appear several months after the onset of jaundice In the cases described the patients had been jaundiced before the skin xanthoma were noted

In some cases of xanthomatous biliary cirrhosis a papulopustular eruption[4 7] (Fig 22) is accompanied by excruciating itching These skin lesions may be believed to be due to scratching It is however evident that the single lesion occurs without scratching even on parts

Lusterman and Montgomery[11] refer in Chart I (case 2) of their paper to a 42-year old man with large liver and spleen xanthoma of the eyelids slight jaundice melanosis and glycosuria Total cholesterol was 536 mgm per cent lecithin 557 mgm per cent, total fatty acids 884 mgm per cent

This author saw in consultation a 40 year old man with xanthoma on the eyelids elbows buttocks and creases of the palm His liver and spleen were considerably enlarged, he was slightly jaundiced and showed a deep bronze pigmentation of the whole body but no glycosuria Total cholesterol was 417 mgm per cent cholesterol present as esters 400 mgm per cent total phospholipids 643 mgm per cent, and lecithin 600 mgm per cent

These three cases can not be classified as xanthomatous biliary cirrhosis The autopsy of the patient of Cantarow and Bucher revealed hemochromatosis of the liver and lymph nodes with extensive hemosiderosis of the pancreas resulting in chronic pancreatitis Most probably the other two deeply melanotic pigmented male patients also had hemochromatosis

Why these patients developed skin xanthoma is a question that cannot be definitely answered The following suggestions may be offered (1) In Cantarow and Bucher's case chronic hemosiderosis of the pancreas may have resulted in secondary hyperlipemia and hypercholesteremia and secondary skin xanthoma An increase of neutral fat in the serum would necessarily be expected if hyperlipemia secondary to chronic pancreatitis was the cause of xanthoma formation in these cases Unfortunately neutral fat has not been estimated in any of these instances* (2) The hemosiderin deposits in the liver may have injured and obliterated the same areas of the finest bile capillaries which this author has described as being concerned with the underlying pathology of xanthomatous biliary cirrhosis The possibility of this second suggestion seems unlikely since neither the jaundice nor the hypercholesteremia nor the hyperlecithinemia were so pronounced as they are in xanthomatous biliary cirrhosis In the future a detailed analysis of serum lipids especially the presence or absence of hyperlipemia (increase of neutral fat) will clarify the etiology of skin xanthoma in such cases of hemochromatosis

Concerning the incidence of xanthomatous biliary cirrhosis in males,

* A case of hyperlipemia and hemochromatosis was recently described by Lehzner and Bowen[1] where the partition of serum lipids showed a moderate increase of neutral fat

Gallstones may complicate the disease but are unrelated to its etiology While the case of Pye Smith[313] shows xanthomatous lesions of the inner lining of the large bile duct, these are, however not regular autopsy findings in xanthomatous biliary cirrhosis The chronic jaundice is therefore not due to obstruction caused by xanthoma formation of the linings of the larger ducts The studies of L MacMahon and Thannhauser[288] on an early biopsy and three autopsies reveal that inflammatory granulomatous tissue, which has already in the early phases of the disease obliterated the finest interlobular bile capillaries causes the permanent jaundice of the obstructive type Indirect and direct bilirubin according to Van den Bergh reaction are found in equal amounts

blood serum

		Normal average
Total cholesterol	1460 mgm %	230 mgm %
Free cholesterol	155	60
Ester cholesterol	1305	170
Total phospholipid	300	2 5
Sphingomyelin	150	25
Cephalin	30	95
Lecithin	21 0	105
Total fatty acids	1970	350
Neutral fat fatty acids	0	0– 00
Neutral fat	0	0– 00
Bile acids	5	none

Serum Chemistry —The diagnosis is established by the clinical history of jaundice of years duration hepatosplenomegaly and the serum analysis for cholesterols, lecithin and neutral fat Characteristic findings for xanthomatous biliary cirrhosis are extremely high figures for cholesterol and lecithin but very low ones for neutral fat For the latter reason the serum is never creamy The ratio of cholesterol cholesterolester is in the first phases of the disease normal i e 70 to 75 per cent of the total cholesterol or even higher The cholesterolester however may drop later according to the condition of the liver parenchyma but the total cholesterol remains high (Case XX) The increase of the phospholipid content of the serum is as characteristic for xanthomatous biliary cirrhosis as the high cholesterols The increase of phospholipids is due to the extremely high lecithin content of the serum The findings of high cholesterol and high lecithin but low neutral fat is pathognomonic for the disease

of the back where scratching is impossible The eruption resembles the lesion of chicken pox

Inflammatory zones of pinkish color surround the nodule The color subsequently changes to bluish red and finally to brownish The nodules which sometimes are not very prominent seem to be situated level with the skin as brownish macula Most of the time a vesicle or small scale is on top of the nodule The crusts which usually cover the healing lesions give the impression of impetiginous ulcers Even if the lesion is not injured there is usually a dark pigmentation This histological appearance is shown in Fig 49

Thannhauser and Magendantz[42] first described this type of maculopapular lesion in xanthomatous biliary cirrhosis together with true xanthoma This type of maculopapular eruption may also appear in chronic hepatitis of long duration

Jaundice —The most outstanding symptom of xanthomatous biliary cirrhosis is jaundice which lasts the entire lifetime of the patient The jaundice may change in degree and periods of very intensive jaundice may alternate with periods of only slight jaundice The jaundice is of the obstructive type and may give the impression of complete occlusion due to a stone in the common duct or to a neoplasm There are times when attacks of pain may also accompany the usually painless jaundice However complete occlusion is never observed Urobilin is found in the light colored feces Many of these patients are operated upon because of diagnosis of obstruction by gallstones or tumor

Liver and Spleen —Liver and spleen are enlarged in size No nodules are felt in the liver There is scarcely a sign of portal obstruction in the skin or in the superficial veins Ascites is therefore not a symptom of this disease but may develop in the final stage A tendency towards bleeding may develop also together with bleeding from gums and intestinal tract In these cases the prothrombin time is lowered Esophageal varices may develop only in the final phase of the disease if portal cirrhosis complicates the disease Attacks of pain may occur during the disease These may be due to gallstones which are not part of the disease but may be accidental occurrences Colicky pains also may be symptomatic of an enlarged liver Recurrent fever customarily found in other types of biliary cirrhosis does not complicate the picture In one of the cases a splenectomy was carried out without any benefit Liver function tests which show positive and negative findings according to the functional status of the liver at the time of examination are of no help in the diagnosis of the disease

Gallstones may complicate the disease but are unrelated to its etiology. While the case of Pye Smith[313] shows xanthomatous lesions of the inner lining of the large bile duct these are, however, not regular autopsy findings in xanthomatous biliary cirrhosis. The chronic jaundice is therefore not due to obstruction caused by xanthoma formation of the linings of the larger ducts. The studies of L. MacMahon and Thannhauser[268] on an early biopsy and three autopsies reveal that inflammatory granulomatous tissue, which has already in the early phases of the disease obliterated the finest interlobular bile capillaries causes the permanent jaundice of the obstructive type. Indirect and direct bilirubin according to Van den Bergh reaction are found in equal amounts.

Blood serum

		Normal average
Total cholesterol	1460 mgm %	230 mgm %
Free cholesterol	155	60
Ester cholesterol	1305	170
Total phospholipid	300	225
Sphingomyelin	150	5
Cephalin	30	95
Lecithin	21 0	105
Total fatty acids	1970	350
Neutral fat fatty acids	0	0– 00
Neutral fat	0	0–200
Bile acids	5	none

Serum Chemistry —The diagnosis is established by the clinical history of jaundice of years duration, hepatosplenomegaly and the serum analysis for cholesterols lecithin and neutral fat. Characteristic findings for xanthomatous biliary cirrhosis are extremely high figures for cholesterol and lecithin but very low ones for neutral fat. For the latter reason the serum is never creamy. The ratio of cholesterol cholesterol-ester is in the first phases of the disease normal i e 70 to 75 per cent of the total cholesterol or even higher. The cholesterolester, however, may drop later according to the condition of the liver parenchyma but the total cholesterol remains high (Case XX). The increase of the phospholipid content of the serum is as characteristic for xanthomatous biliary cirrhosis as the high cholesterols. The increase of phospholipids is due to the extremely high lecithin content of the serum. The findings of high cholesterol and high lecithin but low neutral fat is pathognomonic for the disease.

Bilirubin, as described in section on jaundice, may vary at times but always is much higher than normal Indirect and direct bilirubin are found increased in equal amounts as a sign of obstruction Bile acids therefore are high also In conformity with the other signs of obstruction phosphatase is very high The serum proteins are normal until the final phase

Blood—The patients usually are anemic The kind of anemia is normochromic anemia but becomes hyperchromic in cases of bleeding The elevation of leucocytes is slight usually between 10,000 and 15 000 Blood sedimentation rate is elevated in all these cases

Heart and Blood Vessels—Sometimes the coronaries and aortic valve are involved This condition was reported in early observations by Fagge[110] (1872) and Besnier (1876)[41] Patient H L, Case XV described earlier in this section died of coronary occlusion

Kidney Lungs Brain and Osseous System—These organs are not involved in xanthomatous biliary cirrhosis

Differential Diagnosis

The diagnosis of xanthomatous biliary cirrhosis should be ventured only if all features of this disease are evident In the common variety of biliary cirrhosis neither skin xanthoma nor excessively high cholesterol and lecithin values of the serum are found In simple biliary cirrhosis mostly due to an ascending infection of the biliary tract, periods of elevated temperature interchange with those of normal temperature, while the temperature is normal in xanthomatous biliary cirrhosis

The differential diagnosis for the acute and chronic stage of infectious hepatitis is based on the absence of widespread xanthomatous lesions of the skin and the lipid analysis of the serum Xanthoma of the skin appear in xanthomatous biliary cirrhosis early in the disease together with excessively increased total cholesterol and lecithin values in the serum The percentage of cholesterol present as esters is high in the first years of xanthomatous biliary cirrhosis 70 to 80 per cent In the acute stage of severe hepatitis however the total cholesterol in the serum is never very high and the percentage of cholesterol present as esters is diminished The lecithin values in the serum are not markedly elevated in hepatitis The hepatosplenomegaly becomes more evident in the chronic stage of infectious hepatitis but the serum analysis for lipids does not show a higher level of cholesterol In most of the cases of

chronic hepatitis the total cholesterol formerly elevated in the acute stage has a tendency to decrease and the proportion present as esters remains or becomes low The incidence of skin xanthoma is not mentioned although innumerable cases of acute and chronic hepatitis were reported as epidemics during the war Only in one case observed by Watson Evans and Hofbauer[10] did a male patient show xanthelasma of the eyelid It was not stated however whether the isolated eyelid xanthoma had not already been present before the development of the hepatitis

Eruptive xanthoma" over all parts of the body may occur together with hepatosplenomegaly as a result of various types of hyperlipemia In these cases the hyperlipemia i e an outstanding increase of neutral fat (10 60 times that of normal) is apparent by a milky or creamy non transparent serum already recognized with the naked eye Jaundice despite the presence of hepatosplenomegaly in the hyperlipemic syndromes is not observed The following syndromes belong in this group of primary hyperlipemia with secondary xanthoma (1) idiopathic hereditary hyperlipemia[4, 5, 186, 41], (2) idiopathic non hereditary hyperlipemia with and without slight glycosuria[201] This group includes cases of primary hyperlipemia occurring together with hepatosplenomegaly as described by Buerger and Grutz[6] (3) secondary (transport) hyperlipemia as observed in severe untreated diabetes in chronic pancreatitis[7, 219, 223] or in glycogen storage disease[40, 41, 4, 16] In all these syndromes of primary or secondary hyperlipemia with and without hepatosplenomegaly the creamy hyperlipemic serum and the absence of jaundice immediately exclude a diagnosis of xanthomatous biliary cirrhosis

Skin xanthoma chronic jaundice of slight grade hepatosplenomegaly and considerable increase of cholesterol and moderate increase of lecithin have been reported in the aforementioned rare cases of hemochromatosis It must be admitted that the differential diagnosis of these cases from xanthomatous biliary cirrhosis may cause some difficulty since patients with xanthomatous biliary cirrhosis may exhibit also deep brown pigmentation Hemochromatosis however occurs mainly in males Xanthomatous biliary cirrhosis on the other hand has so far been reported only in females In xanthomatous biliary cirrhosis the extremely high cholesterol and lecithin values are already observed at the very beginning of the disease while in these rare cases of hemochromatosis with skin xanthoma the elevation of the serum lipids and the xanthoma formation occur in the late stages

The liver and spleen in the generalized form of eosinophilic xanthomatous granuloma, Schuller Christian's syndrome synonymous in the literature with normocholesteremic xanthomatosis, lipid granuloma, eosinophilic granuloma) may be enlarged also In these cases jaundice is never present The involvement of the liver and spleen in this group of normocholesteremic" xanthomatosis (eosinophilic xanthomatous granuloma lipid granulomatosis) is part of a systemic granulomatous disorder which may comprise also the skin lymph nodes lung bones dura and liver In xanthomatous biliary cirrhosis however *the liver is the* primary seat of the disease resulting in jaundice hepatosplenomegaly and an outstanding accumulation of cholesterol and lecithin in the serum Xanthoma formation of the skin as well as xanthoma formation of the inner lining of the arteries and in rare cases also of the inner lining of the large bile ducts are secondary to the liver disorder Neither single foam cells nor nests of foam cells however, are found in the liver tissue in xanthomatous biliary cirrhosis

Prognosis

The prognosis in xanthomatous biliary cirrhosis is extremely poor During the first years the patients do not appear very sick and are able to do their work Their chief complaint is a severe itching After several years however, weakness and a tendency to bleed incapacitates them In the final phase portal cirrhosis may develop and complicate the disease Esophageal varices may produce fatal bleeding Atheromatous coronary disease also may be the cause of death A decrease of total cholesterol *together with low values of cholesterol present* as esters is indicative of the last stages of the disease

Treatment

The patient should become a vegetarian since humans do not usually absorb vegetable sterols All kinds of vegetables fruits nuts salads cereals and other carbohydrates are allowed Animal protein should be given only in the form of skimmed milk egg white (no yolk) or cottage cheese Any vegetable fats like olive oil peanut butter pure vegetable margarine can be used for cooking A detailed diet has been outlined see Diet under Therapy of Essential Xanthomatosis of the

Hypercholesteremic Type (Hereditary Hypercholesteremic Xanthomatosis)

In addition intramuscular injections of preparations containing vitamins in ample amounts should be given at least twice weekly since the restriction of meat requires large quantities of vitamin B in these cases of liver damage

This type of diet treatment excludes only the exogenous quota of animal cholesterol but the endogenous production of cholesterol is not influenced and continues For this reason the therapeutic value of such a diet is limited The general nutritional condition during the course of the disease together with the loss of appetite may prompt one to deviate from a strict cholesterol poor diet In such a case small portions of lean meat and lean fish may be added twice a week

The administration of choline methionine and other lipotropic substances is not of great value in this disease since neither increased fat transport (low neutral fat in the serum) nor a fatty liver is observed[48]

2 Rare Cases of Chronic Liver Disease with Secondary Xanthomatosis

The obstruction of the finest intercellular bile capillaries apparently is the cause of a liver cell disturbance resulting in exceedingly high accumulation of cholesterol and lecithin in the serum The possibility exists that areas of the liver where the finest bile capillaries are located become affected not only in xanthomatous biliary cirrhosis but also in other chronic liver diseases

It is surprising that extremely high cholesterol and lecithin values in the serum with the consecutive development of skin xanthoma did not occur in the innumerous cases of epidemic hepatitis observed during the war as well as in cases of chronic jaundice and hepatitis reported as an aftermath of this epidemic of hepatitis A possible explanation may be that in acute and chronic epidemic hepatitis an increased production of cholesterol and lecithin which is suggested as part of the pathogenesis of xanthomatous biliary cirrhosis does not occur

a Hemochromatosis Hypercholesteremia and Skin Xanthoma

Three cases are reported in the literature with hemochromatosis jaundice and hypercholesteremia namely (1) Abel Giraud and Kissel s

case, (1) which erroneously is quoted as a case of hypercholesteremia In fact 1 08 gm were found in 1,000 cm of serum, a figure which equals 118 mgm per cent in 100 cm of serum This case certainly did not show skin xanthoma (2) The case of Dworack[100] according to Sheldon[306] should not be considered as a case of hemochromatosis This case in regard to its clinical features is in the opinion of the author rather to be classified as xanthomatous biliary cirrhosis (3) There remains only the case of Cantarow and Bucher[63], who indeed had skin xanthoma and whose condition was histologically verified as hemochromatosis In this 45 year old male blue grey discoloration of the skin was first noted in 1934 Skin xanthomata were observed four years later 1938 over both upper eyelids the flexor and extensor surfaces of the elbows the palm of the right hand the anterior and posterior axillary folds and on the chest The dull lemon yellow lesions were slightly raised and varied in diameter from - to 10 mm The laboratory findings and the changes found at autopsy especially those in the liver and pancreas of this case of Cantarow and Bucher[63] are described in the following four paragraphs

Laboratory Findings —Total cholesterol was 490, 398, 336 mgm per cent free cholesterol 157 156 106 mgm per cent cholesterol present as esters 333 -4- 106 mgm per cent Serum bilirubin biphasic was 3 -7 0 mgm per cent Urobilinogen in urine was 1 100 to 1 400 There were low normal fasting blood sugar no glycosuria, normal sugar tolerance test

The autopsy showed an unusual quantity of iron in the liver and pancreas in the adrenals in the anterior pituitary lobe and testes

Liver —The capsule was greatly thickened There was a marked increase in the perilobar connective tissue with some invasion of the lobules The latter were much diminished in size and there was wide spread degeneration of the hepatic cells Some areas showed an attempt at regeneration of bile ducts and liver cells Small foci of inflammatory reaction occurred throughout the fibrous tissue containing an enormous amount of brown iron reacting pigment which was also present in the hepatic cells and to a larger extent in the Kupffer cells

Pancreas —No areas of fat necrosis were found Near the head was an extensive area of necrosis and hemorrhage The most marked feature histologically was the extensive infiltration of the pancreatic tissue with a brown iron reacting pigment

Neither total phospholipids nor neutral fat were determined in the serum of the reported cases It is, therefore difficult to decide whether

the hypercholesteremia was due to hemochromatotic liver disease or the result of chronic pancreatitis In the latter condition a considerable increase of neutral fat in the serum should be expected besides the moderately elevated cholesterol and phospholipid values Should however the increase of cholesterol be caused by a liver involvement similar to that of xanthomatous biliary cirrhosis the neutral fat value in the serum should be low and the phospholipids extremely high Future investigations will clarify whether the hypercholesteremia and skin xanthoma in rare cases of hemochromatosis are due to liver disease or to hemochromatosis of the pancreas with resultant pancreatitis

b Postoperative Obstruction of the Common Bile Duct Hypercholesteremia and Skin Xanthoma

The development of skin xanthoma is most unusual in complete obstruction of the common duct Gibson and Robertson[162] report 44 autopsy cases of complete obstruction of the common duct Postoperative complete obstruction was confirmed in 39 of them In none of the 44 cases however were skin xanthoma noted Lusterman and Montgomery[173] described four cases with postoperative stricture of the common duct and skin xanthoma Total cholesterol values in the serum in these were 303 666 793 407 mgm per cent the total phospholipids were 446 46 903 mgm per cent The authors stated that the skin xanthoma disappeared or markedly improved after the restoration of the bile flow to the intestines This condition differs from that found in xanthomatous biliary cirrhosis where the bile flow never is completely interrupted but the skin xanthoma persist permanently Although the level of the total cholesterol is one or two times that of normal in all cases of complete obstruction of the common duct the appearance of skin xanthoma is a rare occurrence

C HYPERCHOLESTEREMIA IN HYPOTHYROIDISM

History

Since the studies of Heckscher and coworkers[1884] in 19 5 it has been known that the cholesterol values in the serum of hypothyroid men and animals are elevated while cholesterol is low in the serum of patients

with hyperthyroidism. It was originally believed that phospholipids and neutral fat[13] show a parallel fluctuation with the increase and decrease of cholesterol in hypo- and hyperthyroidism. Peters and Man[160, 161] however demonstrated that only phospholipids increase and decrease simultaneously with cholesterols. Neutral fat, on the other hand, if elevated at all in hypothyroidism or decreased in hyperthyroidism, does not follow the well recognized pattern of cholesterol. No definite relation exists between the concentration of neutral fat in the serum and that of cholesterol in disorders resulting from hypo- or hyperfunction of the thyroid.

These findings are borne out by the appearance of the serum in hypothyroidism. The serum is transparent and not creamy despite its high cholesterol content. Only three exceptional cases are reported in the literature where a creamy serum occurred together with high cholesterol values and skin xanthoma in hypothyroid patients.

Christie, Lyall and Anderson[8] described a patient with the clinical features of myxedema, creamy serum, high serum cholesterol and skin xanthoma. After thyroid medication the symptoms of hypothyroidism disappeared, the cholesterols in the serum became normal, and the skin xanthoma improved but did not disappear. No figures are reported of neutral fat in the serum before and after thyroid treatment. It is not mentioned whether the creamy appearance of the serum persisted during thyroid medication.

Sweitzer and Winer's case[11] also showed the identical features described by Christie[8]. After thyroid medication the cholesterol level of the serum and the basal metabolism became normal, but the skin xanthoma did not essentially improve. L. S. Craig, H. Lisser and M. H. Soley[94] reported the case of a 49-year old man who had noticed a sudden onset of yellow nodules on his hands and back about eighteen months before his entry to the hospital. His only complaint was fatigue although in response to leading questions he admitted symptoms of hypothyroidism had been present for two years. He denied the existence of all symptoms of gall bladder disease or gastrointestinal disorders. His liver was enlarged to 6 cm below the right costal margin. He had been given thyroid (4 grains) daily for three months with relief from the symptoms including the disappearance of xanthomatous nodules. About three months after this medication was stopped the nodules recurred and continued to enlarge despite sporadic small doses of thyroid. With further treatment with 1½ grains thyroid daily the liver receded to a normal size after one month, and after three months the skin lesions

were regressing The basal metabolic rate varied during treatment from −35 to +8 to −15 Total cholesterol was 9 6 mgm per cent 196 mgm per cent and 340 mgm per cent The serum was creamy Unfortunately there is no report of neutral fat and its fluctuations in the serum during the period of observation nor of the fat content of the food during thyroid treatment

All three patients had a milky serum high serum cholesterol skin xanthoma and the features of hypothyroidism Thyroid treatment decreased the serum cholesterol and improved the clinical features of myxedema considerably However the skin xanthoma did not respond as well to thyroid medication as would have been expected from the effective decrease of serum cholesterols to normal

Pathogenesis

The following possibilities are suggested to explain the persistence of skin xanthoma in hyperthyroid persons whose clinical features of hypothyroidism are cured by thyroid medication The skin xanthoma in these cases are not primarily caused only by hypothyroidism Creamy serum i e high neutral fat in the serum is not a feature of hypothyroidism as Peters and Man[3,4] demonstrated and our own observations confirmed Neutral fat may be slightly elevated in hypothyroidism but not to such a degree that a level 5 10 times greater than normal is reached to produce a creamy serum High neutral fat also is not observed in cases of tuberous xanthoma occurring as a symptom of essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial tary xanthomatosis) There remains only one explanation the assumption that the creamy serum is the primary feature in these three cases and that the myxedematous features aggravated but did not cause the disturbance of fat transportation and fat deposition In other words it is thought that these patients suffered from idiopathic hyperlipemia complicated and aggravated by hypothyroidism A definite decision on this hypothesis cannot be reached because figures are not available to demonstrate that the neutral fat in the serum remained high during the period of thyroid medication It can only be assumed from the fact that the eruptive skin xanthoma did not completely disappear under thyroid medication In the future such rare cases of myxedema with skin xanthoma should be studied first on a fat free diet and thyroid should be given later If the suggested explanation is correct, neutral fat

in the serum will be decreased, and consequently the eruptive type of skin xanthoma will disappear before the myxedematous features are cured by a later thyroid medication

As is evident from numerous observations in typical cases of hypothyroidism only the cholesterol content is markedly increased, while the neutral fat in the serum, if increased at all is only slightly elevated If a creamy serum due to hyperlipemia with eruptive xanthoma whatever its etiology may be, is found, it is exceptional and not typical of hypothyroidism

Etiology

The fluctuations of the cholesterol content in the serum of hypo and hyper thyroid patients depend upon the functions of the thyroid gland as was shown in animal experiments as well as in numerous observations before and after thyroidectomy in men The mechanism influencing the change in the level of cholesterols is not known It is unlikely that the excretion of cholesterol is influenced by the thyroid gland The synthesis of cholesterol from low carbon chains like acetic acid may be under hormonal influence

The thyroid hormone may play a principal part in the control of the regulation of cholesterol synthesis from acetic acid

The rate of exchange of cholesterol from the plasma into the tissue may result in fluctuations of the cholesterol level in thyroid disorders Peters and Man consider the high level of the cholesterol in hypothyroidism as a function of the individual s normal level as well as the result of the disease Since our knowledge of the normal functions of the cholesterol molecule in the organism is so limited neither of the suggested factors which might produce a change in the cholesterol level in the serum in thyroid disorders has any proper experimental foundation

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A IDIOPATHIC HYPERLIPEMIA WITH SECONDARY ERUPTIVE XANTHOMA

1 Idiopathic (Familial) Hyperlipemia in Children with Hepatosplenomegaly and Secondary Xanthoma

Definition

Synonyms—Hepatosplenomegale lipoidose (type Buerger Grutz) and essential hyperlipemia

Definition and Historical Notes—Buerger and Grutz[16] who described a disease in an eleven year old boy in which extreme hyperlipemia was the outstanding symptom designated this condition as hepatosplenomegale lipoidose (lipidosis with hepatosplenomegaly) These authors found that the hyperlipemia as well as the hepatosplenomegaly changed with the fat content of the boy s diet The nodular xanthomatous eruptions present on the external sides of the extremities buttocks face lips and gums appeared and disappeared with the increasing and decreasing hyperlipemia

Opitz[45] reported a case of a twelve year old boy with extreme hyperlipemia and splenomegaly Franklin[5] described a similar occurrence in a five year old girl In both instances there were no xanthomatous eruptions In the paper Idiopathic Familial Lipemia' Holt and his co workers[31] published the case of an eleven year old girl in which hyperlipemia was the outstanding symptom The hepatosplenomegaly was found to change Her mother and three brothers had the same disease but without xanthomatous eruption of the skin Holt and coworkers[31] recognized this disease as a clinical entity different from other forms of hyperlipemia

Goodman Shuman and Goodman[7] observed jointly with the author a two year old boy with marked hyperlipemia hepatosplenomegaly and eruptive xanthoma The nodules were present on the external side of the extremities buttocks ears eyelids and gums Five members of the child s family who were examined did not have hyperlipemia The anatomical findings of this case have been reported by Chapman and Kinney[11] Bernstein with his coworkers[4] published a similar case of idiopathic hyperlipemia with eruptive form of xanthoma in a six year old boy No other member of this family had hyperlipemia

II HYPERLIPEMIA (ACCUMULATION OF NEUTRAL FAT IN SERUM) WITH SECONDARY ERUPTIVE XANTHOMA

General Introduction and Definition

The term hyperlipemia should be exclusively reserved for an abnormal increase of neutral fat in the serum, 'hyperlecithemia' and hypercholesteremia" to designate the increase of these respective lipids in the serum (see chapter on Hyperlipemia) Hyperlipemia usually is accompanied by hypercholesteremia and hyperlecithemia whereas hypercholesteremia occurs without hyperlipemia in essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial xanthomatosis) In xanthomatous biliary cirrhosis (pericholangiolotic biliary cirrhosis) hypercholesteremia and hyperlecithemia are found without hyperlipemia

Secondary xanthomatosis, eruptive form of xanthoma is not a disease entity It is a symptom due to hyperlipemia The different mechanisms producing hyperlipemia may lead etiologically to the eruptive form of xanthoma In contrast to the xanthoma of essential xanthomatosis which do not change much the eruptive form of xanthoma may disappear entirely if the hyperlipemia disappears

In essential xanthomatosis the serum is transparent and not milky Of the lipids only cholesterol and lecithin are increased In secondary xanthomatosis on the other hand a milky serum is the outstanding symptom The neutral fat, which is increased enormously in these instances causes the milky appearance of the serum Cholesterol and lecithin are not increased in the same proportion with neutral fat

There is a distinct histological difference between the xanthoma of essential xanthomatosis and of secondary xanthomatosis Foam cells are sparse in secondary xanthoma There is no granulomatous tissue with giant cells sometimes called Touton cells Extra cellular fat deposits may be visible in the gaps of the inflammatory connective tissue by appropriate staining

The following sections are devoted to the description of the diseases in which secondary xanthomatosis may result from hyperlipemia

Histology of the Eruptive Form of Xanthoma Secondary to Hyperlipemia

In contrast to xanthoma tuberosum in essential xanthomatosis of the hypercholesteremic type the yellow nodules of secondary xanthomatosis do not show nests of foam cells but only a few scattered foam cells (Figs 50 and 51)



Fig 51 Histological picture of a nodule of secondary xanthoma (high magnification) A few scattered foam cells are detected after search (W R case XXIII) Slide through the courtesy of Dr F Parker and Dr F Chapman Mallory Institute Boston Compare with picture of tuberous xanthoma (Fig 6)

There is no granulomatous tissue with giant cells in the nodule of secondary xanthoma Inflammatory tissue with extracellular fat deposits is found in the perivascular lymph spaces The foam cells however are scarce and scattered They stain with Sudan III and Nile blue Lorrain Smith Dietrich staining technic does not give a deep bluish black color

The cases of the above authors are included in this section notwithstanding the fact that only in Holt's case was the familial occurrence of idiopathic hyperlipemia demonstrated The reason for the inclusion of these cases in the familial type of hyperlipemia is the similarity of their clinical features, namely (1) the juvenile age, 1 to 12 years (2) hepatosplenomegaly, (3) abdominal colic, (4) no tendency to glycosuria

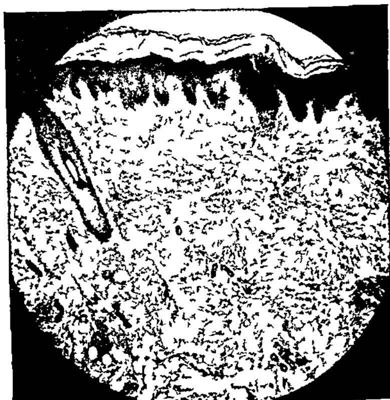


Fig 50 Histological picture of a nodule of secondary xanthoma (low magnification) Note the inflammatory changes and the absence of layers or nests of foam cells (W R case XXIII) By courtesy of Dr Frederick Parker Dr Frederic Chapman Mallory Institute Boston An identical histological picture is obtained in the tissue in secondary xanthoma due to diabetes mellitus (xanthoma diabeticorum)

Ebbe Harslof[7] recently described a sixteen year old boy and his twenty seven year old bother with idiopathic familial hyperlipemia and hepatosplenomegaly These cases belong undoubtedly to the above described syndrome

Pathogenesis

In contrast to essential xanthomatosis of the hypercholesteremic type the foam cells in secondary xanthomatosis are produced by phagocytosis and storage of lipids especially cholesterol as a result of the hyperlipemia The ability of the reticular cells and histiocytes to phagocyte dyes was demonstrated first by Anitschkow and later by other investigators who fed diets rich in cholesterol to rabbits In these experiments

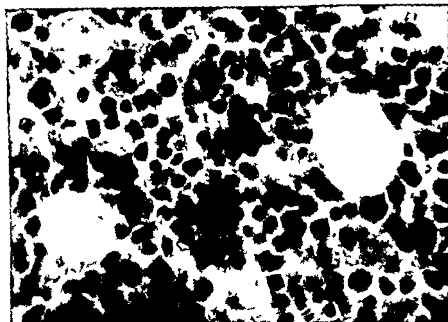


Fig 53 Bone marrow of a child with idiopathic (familial) hyperlipemia with hepatosplenomegaly (W R case XXIII) Note few scattered foam cells Through the courtesy of Dr F Parker and Dr F Chapman Mallory Institute Boston

foam cells were produced which were histologically not unlike those of genuine xanthoma Timothy Leary succeeded in producing skin xanthoma atheromatosis of the blood vessels and arcus senilis of the eyes in rabbits who were fed with animal cholesterol over a long period of time The cells which may have stored cholesterol quite a while release this material after a diet free from cholesterol and fat The hyperlipemia disappears The foam cells however, subsequently undergo destruction and fibrous scar tissue results

Postmortem findings of organs in cases of idiopathic hyperlipemia with hepatosplenomegaly are only described of the patient, observed by Goodman and coworkers and the author This patient died of an intercurrent disease and the autopsy findings are reported by Chapman and Kinney In striking contrast to the high content of neutral fat in the serum, the tissues showed a remarkable lack of neutral fat deposition at autopsy Chemical analysis revealed that the fat content of the organs

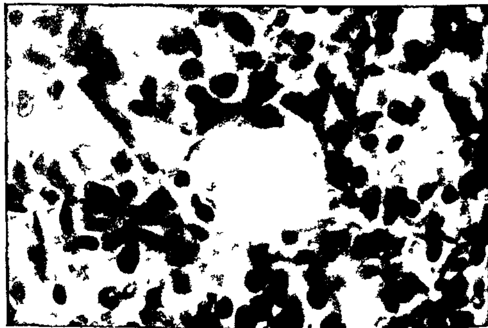


Fig 52 Spleen of a child with idopathic (familial) hyperlipemia with hepatosplenomegaly (W R case XXIII) Note few scattered foam cells identical with large cell hyperplasia of Schultze in hyperlipemia due to diabetes mellitus Through the courtesy of Dr F Parker and Dr F Chapman Mallory Institute Boston

did not exceed the amount found in normal organs Histological examination of the pancreas showed normal structure of the organ and no sign of acute or chronic inflammation Only a few scattered foam cells were found in the liver bone marrow and spleen The histological picture of these three organs was very similar to that in so-called large cell hyperplasia of spleen in hyperlipemia and diabetes (Figs 52 and 53)

assume that the persistent hyperlipemia in these patients is due to an improper mechanism of fat deposition

The mechanism of a defective fat deposition may be caused by anatomical as well as functional changes in the capillaries The latter processes may be affected by hormonal factors The fermentative systems in organs influencing fat deposition and storage may be responsible to some degree

These ferments of the fat tissue are lipases and phosphatases Since the concentration and activity of these enzymes in the serum are a reflection of their concentration and activity in the tissues involved a decrease of lipases in the serum should indicate a corresponding decrease in the fat tissue The absence of lipase in the serum that was observed by the author in the case of Goodman and his associates could not be corroborated in our later experiments with adult cases of idiopathic hyperlipemia At present a hypothesis indicating that a functional disorder of the capillaries causes a retention of neutral fat in idiopathic hyperlipemia (retention hyperlipemia) is the most acceptable explanation

Clinical Cases

Case XXI—An eleven year old girl who demonstrated at the age of four particular skin lesions Holt and his coworkers[20, 21] reported skin lesions beginning as vesicles on the leg and later exulcerating In addition a generalized skin eruption consisting of red scaly discrete lesions was observed on the scalp trunk and extremities This eruption appeared during the summer time and disappeared in the fall Attacks of abdominal pain began a few months after the onset of the skin lesions The sudden pain in the abdomen was followed by projectile vomiting fever abdominal rigidity and collapse After a laparotomy a small amount of yellow fluid was found in the peritoneal cavity No report was made concerning the pancreas The abdomen was drained and the child recovered completely Acetonuria but no glycosuria was noted during her convalescence

Similar attacks subsequently occurred at intervals of several months These were diagnosed as appendicitis gastritis and enteritis by various physicians No further exploration however was attempted The vesicles on the skin i e the skin ulcers still persisted A milky serum was discovered when blood was taken for a Wassermann test when the child was ten Some of the skin lesions were pronounced to be quite typical of psoriasis others resembled ulcers and pustules The liver and spleen were palpable as firm masses the former two finger breadths and the latter one finger breadth below the costal margin There was no abdominal tenderness

While the experimental hyperlipemia produced in animals disappears permanently after a fat- and cholesterol free diet the same experimental findings have not been found in patients with idiopathic hyperlipemia In all the patients observed the hyperlipemia decreased very much but never disappeared entirely Bernstein and coworkers[4] reported that the secondary xanthomatous eruption of the skin had lessened after his patient had been on a diet low in fats In the Goodman case the xanthomatous eruptions cleared up almost entirely In Holt's case[30, 31] the figures for hyperlipemia fell from 4 7 per cent to 2-3 per cent total lipids after a diet low in cholesterol or fat (8 gm per day) In the Bernstein case[4] the figures fell from 9 per cent to 3 per cent after a diet low in cholesterol or fat Despite the severe restrictions of fat in the diet, the serum remained with 4-5 times above the normal values of fat

Holt and his coworkers[30, 31] tried to clarify the pathogenesis of idiopathic hyperlipemia by different experiments They fed their patients thyroxin and injected them with insulin anterio pituitary or liver extract, the hyperlipemia did not decrease Feeding patients choline, which according to Best and his coworkers[7, 8] prevents fatty liver in rats after overnutrition with fat also did not result in a lowering of the hyperlipemia Similar attempts with lecithin and lipocaic' pancreatic extract of Dragstedt and associates were likewise unsuccessful These investigators in addition tried giving patients with idiopathic hyperlipemia transfusions with normal blood on the assumption that a substance was present in normal blood which influences the deposition of fat in the organs of fat storage Although the first transfusion produced a decrease of the total lipids from 4 480 gm per cent to 1 570 gm per cent (normal 100 to 200 mgm %) the following transfusions met with failure These experiments did not give any evidence that the blood contained a hormonal factor which influences the level of blood fat, yet Holt and his coworkers[30, 31] suggested the possible existence of such a substance

Persistent alimentary hyperlipemia results from a sluggish deposition of fatty substances from the capillaries into the organs of fat metabolism and storage In the author's opinion idiopathic hyperlipemia may originate from the same causes as persistent alimentary hyperlipemia but only in an exaggerated way In the section on Hyperlipemia this type of idiopathic hyperlipemia is referred to as retention hyperlipemia The experiments of Thannhauser and Stanely[4] with iodine labelled fat in normals and in patients with idiopathic hyperlipemia show that labelled fat is retained longer in the blood in patients with idiopathic hyperlipemia than in normals (see chapter on Hyperlipemia) It is reasonable to

assume that the persistent hyperlipemia in these patients is due to an improper mechanism of fat deposition

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During the hospitalization of the patient, five of these abdominal attacks were observed all of them essentially similar to the one described and lasting from two to four days The shorter attacks seemed to be accompanied by a higher fever (104 F on one occasion) than the longer ones Pains and collapse were of similar character in both types of attacks With each recurrence an enlargement of the abdominal veins was noticed Following each attack the liver and spleen were found to have increased in size The lipemia and the lipemic appearance of the retina, on the other hand disappeared

Carefully timed chemical observations showed that the critical level for blood fat was 8 per cent When the blood fat exceeded this figure an attack occurred within a few hours The reduction in the blood fat was found to be very rapid and to occur chiefly on the first day of the attack particularly during the first few hours of severe pain when it would be reduced approximately 1 per cent an hour The lowest levels (1 3 per cent to 1 5 per cent) usually were attained on the second day These seldom persisted more than a day or two The serum was milky except when the fat was less than 2 per cent When it was higher than 3 per cent lipemia of the retina became noticeable The hyperlipemia first made its appearance and was always more striking in the peripheral retinal vessels Although the patient took no food during the attack the rapid fall in the blood fat could not be attributed to starvation A later experiment in which the patient was fasted between attacks showed no striking decrease of blood fat

There was no evidence of abnormal excretion of fat either in the urine or stools during an attack On the basis of these findings Holt and his coworkers[30, 31] concluded that the fat recovered from the blood went to the liver and spleen where its accumulation caused an enlargement of these organs the acute distention of their capsules producing the pain They also suggested that some interference with the portal circulation due to an accumulation of fat caused an engorgement of the abdominal veins

Case XXII —Bernstein and coworkers[4] reported a six year old boy who exhibited small pink papules on the face neck and the extremities When the boy was two years old these papules exuded a milky seminviscous fluid While some of these papules were disappearing and others occurring a biopsy was performed on one of these lesions No diagnosis could be made Three years later the lesions gradually disappeared but yellow patches remained under some of the finger- and toe nails At six years of age the child was admitted to the Children s Hospital of Michigan He complained for five days of frequently occurring abdominal cramps of short duration He had no appetite some nausea but no fever during this attack The abdominal pain from which the patient had been suffering was relieved completely by a cleansing enema and did not recur during his period of observation at the hospital A few fine, yellow tinged papules were noted

over the elbows and knees Several small yellow patches were visible under the nails of the great toes and thumbs The edge of the liver was palpable one fingerbreadth below the costal margin The spleen palpated three fingerbreadths below the costal margin felt smooth and hard When blood was taken for Wassermann test the serum had the appearance of rich milk Examination of the eyeground showed the fundi to be normal except that the vessels seemed to be full of milk rather than blood Basal metabolism rate was found normal

Case XXIII—W R A one year old white boy the case of Goodman and coworkers was brought to the hospital in April 1930 because of a



Fig 34 Eruptive nodular papular xanthoma in idiopathic (familial) hyperlipemia with hepatosplenomegaly (W R case XXIII) Note the nodules on the skin of cheeks and tophi like nodules on the ear The nodules are yellowish in color

persistent purulent discharge from the left ear of four weeks duration and a failure to gain weight The family history was negative Father mother and four siblings were living and well The birth was full term and normal the patient weighing seven pounds The prenatal diet was adequate The

child was breast fed for two weeks and then placed on a formula of whole milk water and Karo and at entry was receiving one quart milk plus three teaspoonfuls of cod liver oil daily No cereal orange juice egg or vegetables were included in the diet On admission the patient was unable to sit up without assistance, nor was he able to crawl about He appeared mentally alert There were no previous illnesses except for a persistent muco purulent discharge from the ear of six months duration No history of colic was obtained

Examination revealed a fairly well developed but poorly nourished infant weighing fifteen pounds who did not appear acutely ill Temperature pulse and respiration were normal The anterior fontanelle admitted one and one half fingers the posterior was closed Skin was moist elastic and clear except for an area of dermatitis around the buttocks The tonsils were enlarged On the upper palate there were a few discrete whitish yellow papular lesions There were no teeth A profuse bilateral purulent nasal discharge was present The right ear drum was retracted and thick yellowish green pus filled the left auditory canal There was no post aural swelling The costochondral junctions were enlarged The lungs were normal except for a few transient rales at the bases The heart abdomen and genitalia were negative Liver and spleen were not palpable There were no abnormal neurological findings

During the stay in the hospital an adenoidectomy was done, and the aural discharge gradually subsided The nasal discharge was refractory to therapy but subsided after two months of heliotherapy and nasal irrigations The child was given an adequate diet and gained two pounds while in the hospital

A routine blood Wassermann test revealed gross evidence of lipemia A fasting blood showed an elevated level of total fatty acids of 1 900 mgm / Before further investigation could be carried out, the mother requested that the child be discharged

The patient was readmitted two months and two weeks later because of a progressive yellow papular skin eruption involving buttocks (Fig 56) chin eyelids ears (Fig 54) and mouth (Fig 55) He had been doing well at home now weighing nineteen pounds His appetite was good His diet consisted of one quart of milk daily cereal eggs vegetables orange juice and cod liver oil in adequate amounts Four teeth had developed and he was now able to sit up and stand with support The rhinorrhea and otorrhea had not recurred

Physical examination revealed a well developed and well nourished infant On the buttocks (Fig 56) there were approximately twenty discrete circular and oval papular lesions of a yellow color with an umbilicated top measuring to 6 mm in diameter Similar lesions were found on the thighs scrotum and ears (Fig 54) Those on the eyelids were reddish yellow and resembled chalazion On the hard palate there were many small yellow

papules The liver and spleen were enlarged and palpable two fingers below the costal margin The ophthalmological examination was reported as being consistent with the picture of lipemia retinalis



Fig 55 Eruptive xanthoma on the gums in idiopathic (familial) hyperlipemia with hepatosplenomegaly (W R case XXIII)

At the end of the first week there was no change in the appearance of the lesions The patient then was placed on a low fat diet consisting of skimmed

milk vegetables bread and stewed fruits Cod liver oil and butter were eliminated completely Within a period of one month the lesions on the buttocks scrotum and chin gradually cleared The lesions on the upper palate were still present but fewer in number The spleen decreased in size and was not palpable at the time of discharge Associated with this improvement blood studies revealed a diminution of the total fatty acids (Table XII)



Fig 56 Eruptive xanthoma on the buttocks and around the anus and scrotum in idiopathic (familial) hyperlipemia with hepatosplenomegaly (W R case XXIII)

Clinical Features

Skin—There are two kinds of skin lesions reported in idiopathic (familial) hyperlipemia with splenomegaly The eruptive form of xanthoma was found in three of the published cases This type of eruptive nodular xanthoma is in appearance the same as that described in the literature as xanthoma diabeticorum These carotene like, yellowish colored, discrete papules appear and disappear with the increasing and decreasing hyperlipemia in contrast to tuberous and plain xanthoma of essential hypercholesteremic xanthomatosis which change very little and the existence of which is not dependent upon the hyperlipemia While the secondary xanthomata may develop all over the body, their

preferred location is on the extensor sides of the extremities and on the buttocks They may appear also on the lips palate eyelids and like tophi may in addition be located on the ear and in the skin of the toes Buerger and Grutz[19] described cord like infiltrations which are ivory in color upon pressure, connecting the discrete xanthoma Such an infiltrate also appeared on the under lip of the boy when he was eleven

TABLE VII

Serum	Before fat restricted diet	After fat restricted diet
Total cholesterol	3 9.0 mgm /	330.0 mgm
Free cholesterol	158 5	114 7 "
Ester cholesterol	2 0 5	15 3
Total phospholipid	4 5.0	368 0
Sphingomyelin	12.6 "	1 1
Cephalin	0	60.0
Lecithin	452.4 "	93.9 "
Total fatty acid	3 115.0 "	1,000.0 "
Neutral fat	5	1,495

years old and drained a milky fluid In the Bernstein case[1] the papules exuded a milky semi viscous fluid In the Goodman case the discrete papules disappeared completely after the patient was given a diet low in fats The histological picture in these cases is the same as that described in xanthoma diabeticorum Real foam cells are scarce and search must be made to find them scattered in the tissue Furthermore an inflammatory reaction is seen in the slide There are however no giant cells (Touton cells) like those found in xanthoma of essential xanthomatosis

In addition to the typical nodular eruptive xanthoma a second form of eruptive xanthoma was found in the Holt case[30, 31] Vesicles were observed on the skin of the left leg of Holt s patient They soon ruptured leaving a shallow ulcer persisting for several months This form usually starts with vesicles which soon ulcerate A seasonal increase of these lesions was noted in the summer time There are no foam cells found in this type of a lesion

Liver and Spleen—The outstanding feature of this type of hepatosplenomegaly is the variability in the size of the liver and spleen In Holt s patient[30, 31] these organs increased in size after each attack The size of the liver and spleen increased and the level of blood fats decreased

after an attack of abdominal pain It seemed as if the decrease of the blood fat after an attack resulted in a deposition of fat in these organs In all reported cases the size of the liver and spleen decreased after the patient had been given a diet low in fats In the case the author observed with Goodman both organs returned practically to normal size, when the patient followed a fat-low diet

In Franklin s case puncture of the spleen was performed No abnormal cells were found Some of the large monocytes contained vacuoles but no lipid material or fat Minute patches of sharlich R positive material were scattered all over the film At autopsy the fat content of the liver was not higher than normal The fat was accumulated only in the serum but not in the organs (Table XIIA)

TABLE XII A

	Liver	Normal
Total cholesterol	5 mgm /	2.0 [illegible] mgm /
Free cholesterol	0 73	0.4 0 6
Ester cholesterol	1 79	1 5 2
Total phospholipids	10 05	9 0 11.0
Sphingomyelin	1.44	0 3 1 3
Cephalin	3 0	3.0 5 5
Lecithin	5 5[illegible]	3.0 6 0
Total fatty acids	9.45	8 6 13.0

Abdominal Colic —Colicky abdominal pain occurred in the cases of Opitz[4] Holt[30, 31] and Bernstein[4] No colicky attacks were observed in the Franklin and Goodman cases The pain is localized in the epigastrium and in the midline although it radiates over the entire abdomen Nausea vomiting and vasomotor peripheral collapse produce a serious clinical picture Fever up to 104 F combined with abdominal distension and pain seems to indicate surgical intervention Surgery performed in the Holt case[31] showed only a few c c of yellowish serum in the abdominal cavity There is no report of an inspection of the pancreas during the operation The autopsy findings in the Goodman[7] case showed a normal pancreas All cases do not have abdominal colic It has not been proven and is even not likely that the hyperlipemia as such caused abdominal pain The cause of the abdominal colic in children with idiopathic familial hyperlipemia with hepatosplenomegaly is unknown An involvement of the pancreas as a cause of the attacks is definitely discounted by the autopsy made in the Goodman case , where the pancreas was found normal

Stools and Urine —There is no report of abnormal stools The urine does not contain any fats or lipids Neither sugar nor albumin was found in the cases reported

Blood —In the Holt case[n] the leucocyte count once was as high as 7 300 during the abdominal attack of the patient No severe anemia or change in the white blood cells beyond increase has been reported Blood sugar as well as non protein nitrogen is found normal during the attacks and in the succeeding intervals *There is no increase in bilirubin*

Lipid analysis of the serum in the cases described showed an increase of neutral fat out of proportion to other lipids The serum as a result is characterized by a creamy appearance

The analytical partition of lipids is tabulated in mgm per cent in Table XIII

TABLE XIII

The values are in mgm	Buerger	Opitz	Franklin	Holt	Lemstein	Goodman
Total lipid	94 6	1 880	540	3 0	430	3 934
Total fatty acid	—	—	—	—	—	3 115
Neutral fat	—	—	—	—	—	2 75†
Total cholesterol	686	83	188	3 9	10 9	3 9
Free cholesterol	315	16	—	1	6 7	158
Ester cholesterol	3 6	8	—	0	56	220
Total phosphatides	1 40	8	—	4 0	941	465
Lecithin	—	—	—	—	—	45
Cephalin	—	—	—	—	—	Traces
Sphingomyelin	—	—	—	—	—	1 6

According to the analyses of Thannhauser and Reinstein[47a]

† The neutral fat value was calculated according to the formula of Thannhauser and Reinstein[47b]

The influence of a normal low fat and high fat diet is shown by the figures in Tables XII and XIV

These figures demonstrate that idiopathic hyperlipemia is influenced greatly by dietary treatment which affects not only the level of lipids in the serum but also their composition The neutral fats in the serum are especially subject to the changes produced by the diet The sterols and phospholipids which are not so intensively increased are lowered proportionately The figures in the Goodman case Table XIV reveal that in the increase of phospholipids only the lecithins were involved while the cephalin content on a regular diet was so low that it could not be determined After the patient had been on a diet low in fat the

lecithin was decreased and the cephalin returned to a low normal value The sphingomyelin remained unaltered in normal and low fat diets The low normal figure of sphingomyelin, however, demonstrates that this phosphatide is not involved at all in the mechanism producing idiopathic hyperlipemia with hepatosplenomegaly

In regard to the cholesterols it is evident that, despite the enormous increase in neutral fat the cholesterols are not found proportionately elevated High figures for total cholesterol are reported only in the cases of Buerger and Grutz[16] and Bernstein[4] While in other cases the increase is only in esterified cholesterols the ratio of cholesterol to cholesterol esters in the case of Buerger and Grutz[16] was abnormal These observations may be interpreted only as signifying no damage to the liver parenchyma

TABLE XIV

The values are in mgm /	Holt s case		Bernstein s case			Goodman s case	
	Diet		Diet			Diet	
	Normal	Low fat	Normal	High Fat	Low Fat	Normal	Low fat
Total lipid	7 5,0	590	4 53	9 3,0	3 159	3 954	59f
Total fatty acid	—	—	—	—	—	3 115	1 900
Total cholesterol	3 0	1	541	901	557	3 9	330
Free cholesterol	1	—	1 5	199	1 9	158	1141
Ester cholesterol	0	—	3((	-0	4 8	0	2153
Total phospholipids	4,0	20	51(	833	43(	4(5	368
Lecithin	—	—	—	—	—	453	2059
Cephalin	—	—	—	—	—	Traces	60
Sphingomyelin	—	—	—	—	—	1	12

Blood Vessels —There is no mention of involvement of blood vessels of fatty infiltration of the walls or of atheroma formation in the cases described

Endocrine Glands —There is no demonstrable change in the function of the endocrine glands The basal metabolic rate in the Bernstein case was normal Protein and fat combustion also was normal The patients are not abnormally obese or lean No definite statement has yet been made pertaining to the sexual development of patients with idiopathic hyperlipemia Holt and his coworkers[21] did not mention any abnormality in the family they described

Differential Diagnosis

Hyperlipemia with splenomegaly and secondary xanthomatosis may be confused with xanthomatous biliary cirrhosis In both diseases enlargement of the liver and spleen and xanthomatous manifestations in the skin may be found The most outstanding clinical difference of both conditions is the presence of jaundice of long duration in biliary xanthomatosis and the complete lack of jaundice in idiopathic hyperlipemia with splenomegaly and secondary xanthomatosis These two conditions can be differentiated definitely by the appearance of the serum and the analytical partition of the serum fats In xanthomatous biliary cirrhosis total cholesterol and lecithin are increased out of proportion The neutral fat on the other hand is very low In idiopathic hyperlipemia with splenomegaly however the increase of neutral fat is the outstanding feature Cholesterol and lecithin are found only moderately elevated In xanthomatous biliary cirrhosis tuberous and plain xanthoma on the eyelids elbows and hand do not disappear The eruptive xanthoma secondary to hyperlipemia disappear as soon as the hyperlipemia is diminished Xanthomatous biliary cirrhosis is a progressive severe disease Idiopathic hyperlipemia with splenomegaly is a more benign condition which is mostly discovered by chance

Hyperlipemia with enlargement of the liver is found also in pancreatic hyperlipemia The attacks of abdominal pain and fever in pancreatic hyperlipemia and in idiopathic hyperlipemia are very similar both showing the symptoms of acute peritoneal irritation during abdominal colicky pains The glycosuria and high blood sugar which are found in most cases of hyperlipemia due to intermittent chronic pancreatitis permit a definite distinction between both diseases In instances of chronic pancreatitis where an increase of blood sugar and glycosuria is not found the differential diagnosis may be very difficult The determination of diastase in the urine and blood during the abdominal attacks may be the only differential diagnostic help in such cases The partition of lipids in the serum is of no avail in distinguishing both conditions because the disproportionate increase of neutral fat is also the outstanding symptom in hyperlipemia due to chronic pancreatitis

The hyperlipemia found in a chronic diabetic condition may be easily differentiated from idiopathic hyperlipemia The history of the diabetic disease of longer duration with consequent hyperlipemia and in addition the observation that diabetic hyperlipemia is controlled completely by insulin while in idiopathic hyperlipemia insulin is of no avail facilitate the differential diagnosis in these cases

Hyperlipemia as a result of glycogen storage disease, von Gierke's disease shows the same analytical partition of the serum fats as idiopathic hyperlipemia with hepatosplenomegaly. In both diseases the serum may be creamy or milky. In von Gierke's disease however, only the liver is enormously enlarged, while the spleen is of normal size. These patients have low, and mostly abnormally low, blood sugar. Their sugar tolerance curve is abnormal. Hypoglycemic attacks occur frequently in von Gierke's disease. These two features, large liver and normal spleen, as well as the hypoglycemia are of help in the differential diagnosis between idiopathic hyperlipemia with hepatosplenomegaly and hyperlipemia in von Gierke's disease.

The disease described by Debre and other French authors as "steatose hepatique massive du nourisson" was recognized later as a disease of glycogen and fat storage and named "hepatomegalie polycorique"[170, 1]. The differential diagnosis of this condition and idiopathic hyperlipemia with hepatosplenomegaly is identical with that of von Gierke's disease. Moderate hyperlipemia may be found also in association with hepatosplenomegaly in cases of Niemann-Pick's disease (reticular and histiocytic sphingomyelinosis). The differential diagnosis therefore can not be made by chemical analysis of the serum. The differential diagnosis is evident from the clinical picture. Niemann-Pick's disease which occurs during the first two years of infancy is a rapidly progressing disease with general cachexia (see Part IV of this chapter). Idiopathic hyperlipemia with splenomegaly is observed in children who do not manifest signs of general cachexia. In cases where the differential diagnosis is not so obvious, a bone marrow puncture or biopsy is the decisive factor. It has been assumed erroneously that hyperlipemia is also found in Gaucher's disease (reticular and histiocytic cerebrosidosis). On the contrary, all the lipids in the serum are low in Gaucher's disease. Hyperlipemia is only observed in a mild degree in the last phases of Niemann-Pick's disease.

(2) Idiopathic Hyperlipemia in Adults with and without Secondary Eruptive Xanthoma Occasionally Accompanied by Glycosuria and Hepatosplenomegaly

History and Definition

Early authors who had already noted two different incidents of so-called xanthoma diabeticorum expressed their amazement at the fact

that in some patients the skin lesions of xanthoma diabeticorum increased despite the fact that the urine became sugar free, while in other cases the xanthoma disappeared as soon as the urine became free of sugar. R. Major[41, 41b] recognized that hyperlipemia in diabetic patients is the cause of "xanthoma diabeticorum" (eruptive xanthoma). In his review of the literature he doubted the accuracy of the diagnosis of "xanthoma diabeticorum" in cases reported in the earlier literature (Hutchinson, Robinson and others) because these patients showed creamy serum but no glycosuria. *Although he realized that the hyperlipemia is the cause of* "xanthoma diabeticorum," he was not aware that hyperlipemia may be caused by two entirely different pathogenic mechanisms, namely, transport hyperlipemia (untreated severe diabetes) and retention hyperlipemia (idiopathic hyperlipemia). In both instances eruptive xanthoma (so called "xanthoma diabeticorum") may arise. The clinical syndrome of idiopathic hyperlipemia in adults with secondary eruptive xanthoma *occasionally accompanied by glycosuria* hitherto was *not established as* a clinical entity but often confused with hyperlipemia in severe untreated diabetes and accordingly classified as "xanthoma diabeticorum" or "diabetic hyperlipemia." It has to be stated again and again that this type of idiopathic hyperlipemia is in its pathogenesis entirely different from hyperlipemia secondary to severe untreated diabetes. In idiopathic hyperlipemia with slight glycosuria the hyperlipemia is reduced by a diet low in fat *and does not respond to insulin treatment; in hyperlipemia* secondary to severe diabetes the hyperlipemia is not markedly influenced by a low fat diet but insulin treatment cures the diabetes and simultaneously corrects the hyperlipemic condition. In the first instance the hyperlipemia is *the primary* disorder which *may or may not be accompanied* by glycosuria; in the second instance the diabetes is the primary disorder and the hyperlipemia is the result of a severely disturbed *carbohydrate metabolism. It is therefore necessary to differentiate* idiopathic hyperlipemia accompanied by slight diabetes from symptomatic hyperlipemia in severe untreated cases of diabetes mellitus. No case has been observed where glycosuria accompanying primary idiopathic hyperlipemia has developed into a *more or less definite* diabetic disturbance requiring insulin treatment.

Various cases reported in the literature as "xanthoma diabeticorum" *therefore should be revised in their classification.* McGavack and Shephardson[42] reported two cases of "xanthoma" accompanied by hypercholesteremia occurring in an otherwise normal individual and in an individual with acromegaly and diabetes. Both cases showed definite

Hyperlipemia as a result of glycogen storage disease, von Gierke's disease, shows the same analytical partition of the serum fats as idiopathic hyperlipemia with hepatosplenomegaly In both diseases the serum may be creamy or milky In von Gierke's disease however, only the liver is enormously enlarged, while the spleen is of normal size These patients have low, and mostly abnormally low, blood sugar Their sugar tolerance curve is abnormal Hypoglycemic attacks occur frequently in von Gierke's disease These two features large liver and normal spleen as well as the hypoglycemia are of help in the differential diagnosis between idiopathic hyperlipemia with hepatosplenomegaly and hyperlipemia in von Gierke's disease

The disease described by Debre and other French authors as "steatose hepatique massive du nourisson" was recognized later as a disease of glycogen and fat storage and named hepatomegalie polycorique [0, 1] The differential diagnosis of this condition and idiopathic hyperlipemia with hepatosplenomegaly is identical with that of von Gierke's disease Moderate hyperlipemia may be found also in association with hepatosplenomegaly in cases of Niemann Pick's disease (reticular and histiocytic sphingomyelinosis) The differential diagnosis therefore can not be made by chemical analysis of the serum The differential diagnosis is evident from the clinical picture Niemann Pick's disease which occurs during the first two years of infancy is a rapidly progressing disease with general cachexia (see Part IV of this chapter) Idiopathic hyperlipemia with splenomegaly is observed in children who do not manifest signs of general cachexia In cases where the differential diagnosis is not so obvious a bone marrow puncture or biopsy is the decisive factor It has been assumed erroneously that hyperlipemia is also found in Gaucher's disease (reticular and histiocytic cerebrosidosis) On the contrary all the lipids in the serum are low in Gaucher's disease Hyperlipemia is only observed in a mild degree in the last phases of Niemann Pick's disease

(2) Idiopathic Hyperlipemia in Adults with and without Secondary Eruptive Xanthoma Occasionally Accompanied by Glycosuria and Hepatosplenomegaly

History and Definition

Early authors who had already noted two different incidents of so called xanthoma diabeticorum expressed their amazement at the fact

Eruptive Form of Skin Xanthoma

An eruption of a raised nodular lesion develops rather suddenly and may involve the arms the legs and the trunk mainly on the back and buttocks The face and even the scalp may show some lesions Although they may vary, the nodules are mostly the size of a small pin They may be discrete and as large as a pea or may develop in rows and cords on the skin because of scratching Their color is light yellowish surrounded by a small zone of rose tint discoloration The red zone due to the inflammatory nature of the eruption is caused by distended capillaries The finer nodules which exhibit a yellow top and give the impression of containing pus exude no fluid except blood upon incision Their appearance and disappearance parallels amount of fat in the serum The degree of glycosuria if glycosuria is present at all does not influence their occurrence Itching of the skin is not a constant feature of idiopathic hyperlipemia but may occur only at the time of eruption of the secondary xanthoma

Spleen Eyes and Blood Vessels

Hepatosplenomegaly is rarely found in adults in contrast to children in this type of idiopathic hyperlipemia The liver if enlarged is not a fatty liver and neither the liver nor other organs show an increased deposition of neutral fat However scattered discrete foam cells may be found in the liver spleen and bone marrow Liver function tests are normal The ratio of cholesterol ester may be on the low border of normal 50 to 70 per cent (70-75 per cent is normal) The patients are never jaundiced even if there is hepatomegaly This author saw a case of idiopathic hyperlipemia in the Cushing Veterans Hospital (Dr Maurice Strauss) where an intercurrent epidemic hepatitis caused jaundice While the jaundice and the enlargement of the liver disappeared the hyperlipemia persisted (see case XXVI)

Retina—Patients with idiopathic hyperlipemia show according to the grade of hyperlipemia a milky border of the vessels of the retina (so-called lipemia retinalis")

Blood Vessels—In contrast to familial hypercholesteremic xanthomatosis (essential xanthomatosis of the hypercholesteremic type) the occurrence of angina pectoris and coronary thrombosis is at present not reported in idiopathic hyperlipemia

hyperlipemia (creamy serum) and eruptive xanthoma The first case, a twenty seven year old carpenter belonged without doubt to the group of idiopathic hyperlipemia described in this section The hyperlipemia did not change during the insulin treatment but diminished after a low fat diet In the second case, however of a thirty-three year old negress with hyperlipemia, diabetes and acromegalic features the xanthoma as well as the diabetes improved after insulin treatment The case reported by F Wise and I Garb[1] as 'xanthoma diabeticorum with unusual form of eruption' probably belongs to the group of idiopathic hyperlipemia in adults with eruptive xanthomatosis accompanied by glycosuria

Synonyms—Essential hyperlipemia, xanthoma diabeticorum, hepatosplenomegale lipoidosis type Buerger-Grutz[18]

Histopathology

The pathogenesis and histology of eruptive xanthoma in this syndrome is identical with that in idiopathic familial hyperlipemia (see Figs 50-53 Case XXIII) The foam cell formation secondary to hyperlipemia is the classical example of cholesterol deposition or cholesterol infiltration from the hyperlipemic and hypercholesteremic serum into the macrophagic cells The eruptive nodular xanthoma appear and disappear according to the level of the hyperlipemia

Hyperlipemia

The serum taken in the morning when the patient is in a fasting condition is not transparent but creamy This phenomenon is due to an enormous increase of the neutral fat 10-60 times that of normal (o oo mgm per cent normal) Cholesterols and lecithin also are elevated 2 3 times the normal figures obviously however not in proportion to the excessive accumulation of neutral fat in the serum The level of the serum lipids is dependent upon the intake of fat On a fat free diet the level of serum lipids may become almost normal but rises at once if fat is added to the food again In its behavior the hyperlipemia resembles a persistent postprandial hyperlipemia The neutral fat is believed to be retained in the serum because of a disturbance in the mechanism regulating the penetration of fat through the capillaries into the organs (retention hyperlipemia see Chapter II on Hyperlipemia and Fig 1a)

Diagnosis and Clinical Course

Idiopathic hyperlipemia', if it is not accompanied by eruptive skin xanthoma is for the most part, discovered accidentally at the time of an occasional blood test The creamy appearance of the serum is then called to the attention of the physician by the laboratory technician If an eruption of skin xanthoma develops the creamy serum and its chemical analysis secure the diagnosis Sugar usually is not found in the urine If it is present, a slight restriction of carbohydrate shortly renders the patient sugar-free Hyperlipemia disappears or is reduced to a lower level after a diet low in fat and calories, which also effects the disappearance of the eruptive skin xanthoma A slightly reddish brown discoloration of the skin however remains on the spots where the eruptive xanthoma were located This course contrasts sharply with the behavior of tuberous and plain" xanthoma of the hereditary hypercholesteremic type which do not disappear after diet treatment even if the cholesterol level of the serum is lowered Patients with "idiopathic hyperlipemia must maintain a low fat diet during their lifetime, since excessive hyperlipemia reappears after deviation from the diet As already mentioned insulin is without effect upon the hyperlipemia and the course of the disease The medication with so called lipotropic substances also does not change its course The patients are not handicapped in their activities by the idiopathic hyperlipemia itself Eruption of skin xanthoma may however, cause some discomfort When inflammation of the tissue or exudation like pleurisy as a result of an intercurrent infectious disease occurs in hyperlipemic patients the exudate contains fatty material and becomes milky The resorption of such a fatty inflammatory exudate does not deviate from the normal resorption process The author has seen a severe and unspecific keratitis in a patient with idiopathic hyperlipemia where the infiltrate became fatty in appearance but an opaque scar which was not transparent remained The patient recovered without residual changes (Dr E B Dunphy of the Boston Eye & Ear Infirmary)

Clinical Cases

Case XXIV—S R a 47 year old salesman had noticed one year previously an eruption of yellowish nodules first on his lower arms and then over his whole body This man felt well all the time the skin eruptions appeared and worked without interruption He went to a skin specialist



Fig 57 Eruptive xanthoma in idiopathic hyperlipemia diffused distribution of eruptive xanthoma over back arms and buttocks (case XXIV)



Fig 58 Eruptive xanthoma on elbow forearm and wrist (case XXIV)

(Dr J Swartz of Boston) only because people commented about his hands and face There was no family history of similar skin changes or diabetes When he came under observation an eruptive skin xanthoma (so called xanthoma diabeticorum) was seen on the entire body Face neck trunk buttocks and legs were involved (see Figs 57 and 58) The appearance of the skin xanthoma was the same as that already described In addition there were yellowish hyperkeratotic wart like formations on both palms and the lateral sides of the feet The eruption of xanthomatous nodules forming peculiar cord like nodules followed the pattern of skin lacerations caused by scratching The patient at this time showed so called lipemia retinalis

Physical and Laboratory Examinations—Weight [illegible]03 lbs Lung and heart showed no abnormal findings no murmur Blood pressure was 140/90 Liver and spleen visualized by a flat film of the abdomen were reported as slightly enlarged Hemoglobin 1[illegible]3 per cent = 19 1 gm Red blood cells 6 150 000 color index 0 99 white blood cells 7 500 blood sedimentation rate [illegible] mm in 1 hour

For blood chemistry findings see Table XV

Case XXV—H Z a [illegible]6 year old taxi cab driver first noticed discrete small yellow nodular eruptions on his forearms five months ago These spread to the trunk buttocks and legs He was not bothered by itching and had no other complaints He is only ashamed to show his rash while bathing He is not married He has a good appetite No family history of diabetes or other metabolic disorders

The eruptive skin xanthomata have the same appearance as those already described in Case XXIV They are discrete yellow nodular lesions with a slight inflammatory halo around the eruption *Physical Findings*—A 196 lb healthy looking young man has normal lungs and heart blood pressure 120/90 Liver and spleen are not enlarged Eyeground shows slight lipemia retinalis Basal metabolic rate is minus 10 Urine shows no albumin and no sugar Fasting blood sugar is 115 mgm per cent Hemoglobin is 104 per cent or 16 gm red blood cells 5 190 000 color index 1 0 white blood cells 11 300 blood sedimentation rate 16 mm in one hour The blood serum is creamy in appearance For serum analyses see Table XVI

Case XXVII—H McN male [illegible] years old was seen at the Cushing Veterans Hospital through the courtesy of Dr Maurice Strauss The patient was hospitalized because of epidemic hepatitis At this time his liver was considerably enlarged His spleen was not palpated with certainty He recovered slowly from the hepatitis When the lipid analysis of his serum was made the jaundice had disappeared almost completely He was out of bed and felt healthy He did not show eruptive skin xanthomata The creamy serum persisted after his discharge No signs of chronic liver disease were present For serum analyses see Table XVII

TABLE XX

Lipid and Sugar Analyses of Serum of Case XXII

	1 1946	9 1946 After a low fat diet	6 4 46		9-19 46	1 10 47	19 47	Remarks
Total fatty acids	5196 mg %	480 mg %	688 mg %		1171 mg	1310 mg	3100 mg	*6 5 46*
Neutral fat	4477	275	350		——	964	[illegible]	The eruptive xanthoma disappeared
Total cholesterol	693	175	9	The patient gradually stopped keeping to his diet	4	318	575	gradually and were completely gone
Free cholesterol	523	58	76		85	1 0	150	leaving a brownish red skin discoloration
Cholesterol present as esters	396 (53 of total)	117 (6, of total)	16 (,4 of total)		185	181	[illegible] (60 of total)	
Total phospholipids	810	195	50		——	318	551	*5 19 47*
Lecithin and cephalin	685	175	220		——	——	——	The eruptive xanthoma had not yet
Blood sugar	06	150	124		1 0	——	——	reappeared
Urine sugar	0 gm	Negative	Negative		Negative	Negative	Negative	

TABLE XVI

Lipid and Sugar Analyses of Serum in Case XXI

	1 47		7 47
Total fatty acids	2994 mg	Patient did not	4080 mg %
Neutral fat	234	adhere to his	3632
Total cholesterol	5 5	diet at all	486
Free cholesterol	2 1		272
Cholesterol present as esters	304 (58 of total)		214 (44 of total)
Total phospholipids	563 mg		657 mg %
Lecithin and cephalin	----		580
Blood sugar	115		----
Urine sugar	Negative		Negative

TABLE XVII

Lipid Analysis of Serum in Case XXII

	3 11 41		4 47
Total fatty acids	33 0 mg	After a low fat	1840 mg %
Neutral fat	320	diet	1612
Total cholesterol	250		204
Free cholesterol	150		86
Cholesterol present as esters	100 (40% of total)		118 (58 of total)
Total phospholipids	328 mg		207 mg
Lecithin and cephalin	90		----
Blood sugar	----		----
Urine sugar	Negative		Negative

Case XXIII —H B H a 34 year old man was admitted on June 3 1948 to the hospital because of an easy fatiguability and pimple like eruption on his face legs and arms He had been in excellent health until December 1947 While refereeing a basketball game he noted weakness in his legs Some sugar was found in his urine His infected lower teeth were removed The sugar disappeared until January 1948 when it reappeared He was advised to reduce the starches and sugar in his diet After losing five pounds his weight remained constant Four weeks before his admission to the hospital his skin broke out with raised yellow lesions which were bothersome The lesions did not discharge The patient's past history was not remarkable there was no family history of diabetes

Physical examination revealed a slender adult whose whole body was covered with scattered raised yellowish lesions with a slightly inflammed base They were specially marked on the elbows knees and buttocks The

pupils reacted to light and accommodation Fundi showed lipemia retinalis Discs were normal Lungs and heart normal B P 110/80 Pedal pulsations on both sides were good Urine on 6 15-48 clear, straw colored acid Specific gravity 1 035 Sugar + + Acetone + Blood 4 340,000 red blood cells 1 00 white blood cells Sedimentation rate 4 Basal metabolism +14

During the hospital stay the patient did not feel sick He was put on a diet low in carbohydrates and calories The skin lesions disappeared almost completely after diet treatment Fasting blood sugar 6 15 48 175 6 18 48 155

TABLE XVIII

Lipid Analysis of Serum in Case XXVII

Total fatty acids	7 00 mg %	
Neutral fat	6,570	
Total cholesterol	900	
Free cholesterol	403	
Cholesterol present as esters	497	(55% of total)
Total phospholipids	400	
Blood sugar	175 (6 15 48)	
	155 (6-18 48)	

Differential Diagnosis

1) The differential diagnosis from essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial xanthomatosis) may not be so obvious in some cases as Cases XXIV and XXV If the eruptive skin xanthoma last for a long while the inflammatory character of the lesion i e the red area around the lesion may disappear The remaining yellow lesion can hardly be discriminated from a 'tuberous or plain lesion of the hereditary hypercholesteremic type' In such cases the character of the serum milky or not, and the quantitative analysis for neutral fat is decisive In idiopathic hypercholesteremia neutral fat is outstandingly elevated unproportionally so to cholesterol and phospholipids In hypercholesteremic familial xanthomatosis the cholesterols are mainly elevated while the neutral fat is not at all or slightly elevated in the serum The xanthoma in idiopathic hyperlipemia disappear after a fat-free diet while in familial hypercholesteremic xanthomatosis they are permanent and change little

2) The differentiation of 'idiopathic hyperlipemia with secondary xanthomatosis occasionally associated with glycosuria and hepatosplenomegaly from idiopathic familial hyperlipemia with secondary xantho

matosis and hepatosplenomegaly is rather arbitrary since in the latter condition the familial character was not demonstrable in some of the reported cases However the clinical syndrome abdominal colic the definite hepatosplenomegaly the sickly appearance of the children justifies the differentiation of this syndrome from idiopathic hyperlipemia of adults which occurs without any discomfort and usually is only accidentally detected

3) The hyperlipemia with eruption of skin xanthomata found in chronic severe diabetes is differentiated easily from the idiopathic hyperlipemia by the history and clinical findings of severe diabetes and ketosis Insulin treatment controls the diabetic disturbance and the hyperlipemia disappears at the same time or is considerably reduced In contrast to idiopathic hyperlipemia a diet low in fat does not influence diabetic hyperlipemia

4) In cases of chronic pancreatic diseases with hyperlipemia the hyperlipemia always is associated with clinical symptoms of pancreatic involvement while in idiopathic hyperlipemia of adults the individual is a healthy person mainly with no complaints hinting of an organic disease

Prognosis and Treatment

The fact that no autopsy findings have been reported in cases of patients suffering from idiopathic hyperlipemia seems to favor a good prognosis An early development of atheromatosis as a consequence of hyperlipemia of years duration may change the favorable life expectancy of the patient The only necropsy reports are those obtained from the Goodman patient[2] who died of an intercurrent disease Idiopathic familial hyperlipemia with hepatosplenomegaly and secondary xanthomatosis as well as idiopathic hyperlipemia of adults accompanied by glycosuria have been recognized as clinical entities only recently As a result knowledge concerning the further development and progress of the disease in patients who are alive but not under constant observation is limited Idiopathic hyperlipemia with hepatosplenomegaly is certainly not a rapidly progressing disease The fate of the liver in later stages is still unknown The fact that the size of the liver and spleen correspondingly increases and decreases with the level of the lipids in the serum may indicate that a persistent accumulation of fat in the serum does not cause irreparable damage in the liver

The definite influence of the diet on the level of fats in the serum of

patients with idiopathic hyperlipemia has been shown in all the cases described to date A diet low in fats has to be prescribed for these patients Since animal cholesterol is present not only in fats but also in meats proteins derived from vegetables, skimmed milk and egg white, which are low in animal cholesterol are preferable Protein and carbohydrates should be the main constituents of the diet Vitamins may be added according to the individual need

DIET

Menu for Idiopathic Hyperlipemia

CHO	PRO	FAT	CALORIES
[illegible]5	1[illegible]0	[illegible]0	1560

BREAKFAST	Juice of [illegible] oranges with [illegible] egg whites ½ cup (30 gm) rolled oats 1 slice of whole wheat bread 8 oz skimmed milk
MID MORNING	6 oz grape juice with two egg whites
LUNCH	[illegible] oz of white meat of chicken or white fish (cod sole halibut or haddock) green salad (lettuce tomatoes carrot strips etc) 1 slice of whole wheat bread baked apple with meringue of 2 egg whites 8 oz skimmed milk
MID AFTERNOON	6 oz orange juice with 2 egg whites
DINNER	¼ lb broiled chicken or white fish as at noon 1 medium baked potato ½ cup string beans ½ banana 8 oz skimmed milk
BEFORE BED	6 oz fruit juice with 2 egg whites

Holt and his coworkers[31] added 5 gm of lecithin and choline to his patients daily diets without producing any change in the hyperlipemia The administration of other lipotropic substances like inositol and methionine are not of help Thyroxin anterior pituitary extract and liver extract also were ineffective

Because it was believed that normal blood especially after meals may contain a factor which regulates the deposition of fat the patients were given blood transfusions This experiment likewise did not fulfill the investigator's (Holt) expectations Dragstedt's lipocaic pancreatic extract was applied for three weeks without any convincing results

The most difficult problem confronting the physician is the decision of surgery in cases where abdominal colics fever and signs of peritoneal

irritation are alarming in idiopathic familial hyperlipemia in children Surgery should not be advised if the diagnosis of idiopathic hyperlipemia (creamy serum) is established as the etiological factor of the abdominal colics

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B SYMPTOMATIC HYPERLIPEMIA WITH SECONDARY ERUPTIVE XANTHOMA

1 Hyperlipemia in Severe Uncontrolled Diabetes with Secondary Eruptive Xanthoma

Definition and Historical Notes

Eruptive secondary xanthoma occurring in diabetes is known as xanthoma diabeticorum

The occurrence of hyperlipemia in diabetes mellitus was mentioned by Mariet[13] of Edinburgh (1799) Traill[23] (1823) found 4.5 gm % Lecanu[7] 11.7 gm % and Neisser and Derlin[17] (1903) 19.7 gm % material extractable with ether from the blood

The first description of eruptive xanthoma in diabetes mellitus was published by Addison and Gull[1] (1851) Since then the numerous observations which have been reported definitely show that eruptive xanthomata occur in diabetic patients exhibiting high cholesterol values and hyperlipemia at the same time

Pathogenesis

Hyperlipemia in severe diabetes results from a disturbance of the carbohydrate disintegration in the liver Fat consequently is transported and accumulated in this organ for combustion and hyperlipemia results secondary to fat transportation As soon the liver is able to disintegrate carbohydrate sufficiently, the hyperlipemia and the eruptive xanthoma as well as the fatty liver disappear The restoration of this function is achieved by the application of insulin Many examples of these changes have been reported not only in patients but also in animals with experimental diabetes

This kind of hyperlipemia occurring in patients with severe diabetes was reported frequently in the older literature especially before insulin was made available Today such cases are observed rarely because insulin is given as soon as the diabetic condition is recognized

The type of hyperlipemia occurring in severe cases of diabetes is thought to originate from transport of neutral fat to the organs of metabolism (see transport hyperlipemia)

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June 1 1949

There was also an eruption characterized by nodular pustules surrounded by narrow pink zones The lesions disappeared within five months after the patient had been given insulin and diet treatment As a result of the insulin treatment the hyperlipemia and hypercholesteremia completely disappeared

Date	*Cholesterol*	*Blood Sugar*
1/15/34	1 600 mgm %	0 1%
1/16/34	1 5 0	0 1
1/17/34	1 344	
1/18/34	1 3 6	0 1
1/19/34	1 48	0 21
1/ 0/34	1 48	0 7
1/ /34	1 184	0
1/ 7/34	9	0 19
/ 3/34	416	0 15
/17/34	94	0 18
3/15/34	175	0 19
5/ 3/34	17	0 6
6/ 9/34	05	0 16

Case XXIX —This patient and another similar case were studied by Freda K Herbert[1] and reported in a paper Observations on Blood Fats in Diabetic Lipaemia The figures reported in gm per cent have been changed in this chapter to mgm per cent for comparison with other cases in this section

R W male age 25 was admitted to the Newcastle General Hospital in March 1934 He had been treated for diabetes for 6 months with insulin and dietetic measures but shortly before admission had indulged in large amounts of carbohydrate No unusual amount of fat had been taken On admission he had glycosuria and intense ketonuria and the fasting blood sugar was 312 mgm per cent The whole blood had the color of chocolate The plasma separated quickly and had the appearance of cream Lipid analysis Table XIX

TABLE XIX

First Series of Observations on Case XXIX

		4 5 hours after breakfast and insulin		
	3 2 34	3 23 34	4 10 4	4 14 34
Total fat of plasma	22 000 mg	18 00 mg	10 mg	1 870 mg %
Lecithin of plasma (calculated from lipin P)	950	——	——	——
Cholesterol of plasma	1,410	1 310 "	"	——
Cholesterol of corpuscles	——	——	160	——

Morbid Anatomy

Fischer (1903) in his paper on lipemia and cholesteremia with pathological findings in the pancreas and liver especially emphasized the fact that the cirrhotic changes of the pancreas as well as the changes of the Langerhan's islets were etiologically important features of hyperlipemia. Schultze[9] was the first to describe "large cell hyperplasia" of the spleen during diabetic hyperlipemia. He showed that small nests of xanthoma cells (foam cells) occur in the spleen as a result of the hyperlipemia in diabetes mellitus. The presence of foam cells in the liver as well as the spleen was confirmed by many later investigators as a characteristic feature of diabetic hyperlipemia.

Lubarsch[8] described the most outstanding example of this group of secondary xanthomatosis. The patient, who had for a long time suffered from diabetes mellitus with hyperlipemia, died in a coma. Large patches of xanthoma cells were found in the liver, spleen, the walls of the lymph vessels and especially the lymph nodes (xanthomatous lymphangitis). The skin, however, showed no yellow nodules or other manifestations of secondary xanthoma. There was, however, xanthosis which is due to carotenemia but not to secondary xanthomatosis.

This case demonstrates that "large cell hyperplasia", foam cell formation as a secondary process to diabetic hyperlipemia, may be widespread. Not only the spleen but all the organs which contain phagocytic cells and macrophages may become involved in the process of secondary cholesterol deposition resulting from hyperlipemia. The different mechanisms of xanthoma cell formation become evident in essential xanthomatosis and in secondary xanthomatosis due to hyperlipemia. In the latter case large cell hyperplasia and foam cell formation are due to phagocytosis and deposition of cholesterol into the cell. In essential xanthomatosis the accumulation of cholesterol within the cell is due to a disturbance of the lipid metabolism within the cell and not to a deposit of cholesterol from the blood stream.

Clinical Cases

Case XXVIII—A. N.* When the patient was first seen by Dr. Joslin in January 1934 he had acidosis. Glycosuria 7.4 per cent. Blood sugar 50 mgm. per cent. Insulin 56 units daily. The patient had lipemia retinalis

* The author is indebted to Dr. Elliot P. Joslin and his associates, Deaconess Hospital, for the privilege of using this case.

In May 1936 an unmarried Englishwoman aged 26 consulted the skin department about a rash which had been present for two months mainly on the arms knees and neck This was recognized as papular xanthomatosis heavy glycosuria was discovered and she was referred at once to the diabetic clinic for treatment Here a pale clear urine was found to contain 6.4 per cent of sugar no ketone bodies and a moderate cloud of protein on boiling The blood contained 364 mgm of glucose per 100 ml cholesterol 417 mgm per 100 ml and total fat 6 volume per cent (lipocrit) which separated as a thick cream on standing She was admitted to the hospital for treatment and investigation of the diabetes and lipemia

In childhood she had had mumps and German measles but no serious illness in all her life There was no family history of diabetes or metabolic disease She was an only child her mother aged 65 was alive and well her father had died at 5 from encephalitis

The history of her present illness showed classical diabetic symptoms with a loss of 12 lb in this time and with a xanthomatous rash for two and a half months Otherwise she felt energetic and fit for her work as a telephonist Menstruation was regular and normal Clearly diabetic symptoms preceded overt manifestations of lipoid disturbances by many months Her normal appearance and photograph taken four years earlier make it unlikely that her disease was of long standing

Physical examination showed nothing abnormal (pulse rate 70 per min blood pressure 110/70 Mg) except lipemia retinalis widespread eruptive xanthomatosis and general thinness In a 3 inch wide area of the right upper arm 1 o slightly raised yellow macules without any inflammatory ring were counted The knees and the neck were also richly covered with them but the rest of the body was unscathed No enlargement of the liver and spleen was present at first

In the hospital the diabetes rapidly cleared on only 20 units of soluble insulin daily and she returned to work in a week feeling well and gaining weight She needed more insulin soon 50 units a day and in four months the skin rash had disappeared although slight lipemia persisted She was not seen again for over a year when in January 1938 she was noted to have a bulging abdomen and a very large liver and spleen By the end of the year the basal metabolic rate was found unexpectedly to be very high and progressive lipodystrophy became more and more obvious

Thyroidectomy was undertaken in June 194 with no clear preconception of what would result Her physicians were encouraged by the patient s adventurous attitude She was tired of her condition and long stay in the hospital and has seen dramatic improvement in thyrotoxic diabetics from the operation

For some weeks before operation the patient had been on 160 units of insulin a day She had lost much weight and was intensely lipemic (cho

Under treatment by diet and insulin the lipemia and hyperglycemia were controlled During the period of recovery a special diet was given in order to compare the fats of the food with those of the blood This was started on Aug 7th and continued until Aug 14th two blood samples being taken during this time (Table XIX) During the same period the average daily excretion of fat in the feces was 5 5 gm The experimental diet contained 55 gm protein 1 0 gm carbohydrate and 106 gm fat daily

The patient recovered and was discharged when a proper balance of diet and insulin had been established

In the following August he again took excessive carbohydrate but no undue amount of fat and was re-admitted to the hospital in coma with severe ketosis and a fasting blood sugar of 56[illegible] mgm per cent There was lipemia again the plasma fat being 9 120 mgm per cent and the cholesterol 1 100 mg per cent (Table XX) For the first four days he was treated with insulin and glucose and as soon as he began to take food he was given the same experimental diet as had been used before This was continued throughout the period of the analyses given in Table XX except for an interval between August 7th and 10th when some bacon fat was given instead of butter

TABLE XX

Second Series of Observations on Case XXIX

Conditions	No food Insulin and glucose	[illegible] hours after breakfast and insulin			
Date	[illegible] 30 34	8 [illegible] 34	8 7 34	8 1[illegible] [illegible]4	8 17 34
Total fat of plasma	[illegible]1[illegible]0 mg	4 680 mg %	4 [illegible]0 mg %	2 860 mg %	4[illegible]0 mg
Lecithin of plasma	[illegible] 0	——	——	——	——
Free cholesterol of plasma	520	——	——	——	——
Total cholesterol of plasma	1 100	640	[illegible]40	520	410

Again the condition was controlled by treatment and lipemia diminished The patient was discharged on a balance regime of diet and insulin

In March 1935 another breach of diet was followed by coma A blood sample taken during recovery under treatment with glucose and insulin showed only faintly turbid plasma and the cholesterol was 349 mgm per cent

Case XXX — This case was studied by R D Lawrence and reported in a paper Lipodystrophy and Hepatomegaly with Diabetes Lipaemia and Other Metabolic Disturbances [illegible] This rather exceptional case deserves to be quoted in detail because hyperlipemia due to severe diabetes was present together with unusual features such as localized circumscribed atrophy of the subcutaneous fat tissue of the face and legs enormous enlargement of the liver spleen and lymph nodes

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For some weeks before operation the patient had been on 160 units of insulin a day She had lost much weight and was intensely lipemic (cho

lesterol 770 mgm per ml) This was corrected by 960 units of insulin a day (given four hourly) and the patient was brought to the theatre with a normal blood sugar no ketosis The lipemia was reduced

Mr John Hunter removed the thyroid almost totally, and the recovery phase was fairly smooth For a few days after the operation the patient was somewhat sick and unable to eat her carbohydrate and insulin had to be reduced to 160 units a day but quickly was increased to 360 units again During this phase an optimistic house physician thought the liver was smaller and softer but I (D Lawrence) remained skeptical As time went on it became clear that thyroidectomy had made no difference in her general organic condition or to the diabetic or lipid metabolism

After operation the basal metabolic rate fell gradually, until it reached plus 38 at the twelfth week She gained 7 lb and gradually developed a painful stiffness in all her muscles which became intolerable The girth of the calf was increased and the electrical reactions to a single galvanic stimulus showed a slower contraction and a more prolonged relaxation than normal muscles There was no obvious subcutaneous or skin changes and no noticeable changes in the hair voice or pulse rate but it seems clear that she was developing symptoms of hypothyroidism although the basal metabolic rate was much above normal The metabolism was raised by giving thyroid gr a day and the pains were alleviated but it required gr 3 to make her feel quite well and this restored her basal metabolism rate to +0% She remained on this dose and at this metabolic level during the succeeding year For the last six months of her life she felt in excellent health She took 640 units of insulin a day never had hypoglycemia and remained vigorous in spite of her constant lipemia considerable hyperglycemia a huge liver and spleen and a complete absence of subcutaneous fat

Terminal Illness—In August 1943 although still in vigorous health and full employment the patient complained that her abdomen was uncomfortably fuller The liver and spleen seemed the same but a new cystic swelling was felt near the bladder This enlarged rather rapidly and by October was diagnosed as a large ovarian cyst

Our doubts about operation were finally decided by intolerable abdominal distension and in December two large bilateral ovarian cysts and the appendix were removed The cysts were simple serous cysts lined with low columnar epithelium with a few shallow invaginations into surrounding dense fibrous stroma (At operation biopsy material from liver spleen pancreas and muscle was obtained in a normolipemic phase) After operation great difficulties arose from pain and vomiting was frequent but her usual carbohydrate was administered often intravenously The insulin requirements fell greatly and some days as little as 80 units kept the urine completely sugar free The abdominal tension stitches would not hold the wound gaped twice and became infected and serious hemorrhage occurred

The urine too became heavily infected with *B coli* and enterococci and in spite of blood saline and glucose transfusion she died suddenly three weeks later after a few days pyrexia of 103° F with rigors Only 40 units of insulin was given at 6 A M that morning after which she had taken glucose drinks well The blood sugar at noon was only 53 mgm per 100 ml This may have contributed to her death at 5 P M but 60 gm of glucose was given intravenously at . P M without any recovery from increasing unconsciousness I (D Lawrence) have seen similar reduction of insulin requirements in other diabetics at the ebb of life

The details of the metabolic studies should be read in the original paper R D Lawrence summarizes the clinical and autopsy findings as follows

A unique case of a young woman is described who over seven years developed complete lipodystrophy a huge liver and spleen and enlargement of the parotids and all the lymph glands Strange metabolic disturbances accompanied this severe diabetes intense lipaemia and an extremely high basal metabolic rate over +50,

The pathological findings confirmed complete absence of subcutaneous and retroperitoneal depot fat and showed portal cirrhosis duct proliferation in the parotids and a peculiar dilation of the sinuses of the lymph glands All the endocrine glands were essentially normal and also the cellular and chemical blood picture

Metabolic studies showed a sever diabetes unusual in its extreme insulin resistance (maximal control dose 000 units) absence of ketosis and normality of the pancreas The lipaemia was variable (maximum 8%) but the proportion of the various blood lipids remained constant at all levels and the fat-content of the liver and other internal organs was normal *The lipaemia was independent of dietary fat but directly dependent on the blood sugar concentration* A high blood sugar level always led to lipaemia whereas a low blood sugar level abolished it The high metabolic rate (maximum +170) was not due to thyrotoxicosis but thyroidectomy reduced the rate +40% at which level myxedema developed [1]

Clinical Features

Skin—Addison and Gull[1] gave the following description of the eruption of xanthoma diabeticorum The eruption somewhat suddenly appeared on the arms In the course of ten days it had extended over the arms legs and trunk both anteriorly and posteriorly also over the face and into the hair it consisted of scattered tubercles of various sizes some being as large as a small pea together with shining colorless papules They were most numerous on the outside and back of the fore arm and especially about the elbows and knees where they were con

fluent Along the inner side of the arms and thighs, they were more sparingly present, and entirely absent from the flexures of the larger joints Besides the compound character produced by the confluence of two or three tubercles, which appeared to be such as shown by the prominent whitish nodules upon them, some looked as if they were beginning to suppurate, and many were not unlike the ordinary molluscum, but when incised with a lancet they were found to consist of firm tissue which on pressure gave out no fluid save blood

They were of a yellowish color, mottled with a deepish rose tint and with small capillary veins here and there ramifying over them They were accompanied with a moderate degree of irritation, hence the apices of many were rubbed and inflamed "

As is evident from the classic description of Addison and Gull, the appearance of the eruptive xanthomatous nodules in diabetes is the same as that in idiopathic hyperlipemia'

Xanthosis (carotene coloring of the skin), especially of the palms and soles is found in some instances The occurrence of xanthosis in cases of diabetes mellitus, as well as in cases without diabetes, indicates that the carotene is increased in the serum (normal value 02 mgm per cent) The significance of the increase of carotene in cases where high cholesterol values are found also in the serum is not known Although carotene and cholesterol are chemically entirely different substances they travel together with fat Carotene is taken in with the food, especially carrots and spinach but is not built up in the organism It is excreted in the bile

Liver—The liver may be enlarged Its size changes with the level of the hyperlipemia In some instances the liver always remains firm and large Function tests do not reveal any greatly impaired function

Spleen—During the lifetime of the patient the spleen usually is not felt At autopsy the size of the spleen is found larger than normal Microscopic examination reveals 'large cell hyperplasia i e scattered foam cells in this organ

Diabetes Mellitus—Hyperlipemia and the eruptive form of xanthoma were believed formerly to be symptoms of acidosis and severe diabetes Major[10, 11] pointed out that this was not the case and that the eruptive xanthoma are the result of the hyperlipemia

The injection of insulin always balances the diabetic condition even though it may be produced by etiologically different factors In cases of hyperlipemia due to a primary disturbance of the carbohydrate metabolism the glycosuria hyperlipemia and xanthomatous eruptions disappear simultaneously after insulin treatment

In cases of hyperlipemia due to chronic pancreatitis insulin balances glycosuria The secondary xanthoma *may disappear temporarily* The hyperlipemia and hypercholesteremia are however not influenced by insulin (see next section in this chapter)

Blood Vessels—Diabetic patients *suffering from hyperlipemia* and hypercholesteremia are early doomed to become subject to atheromatosis and arteriosclerosis Arterial occlusion which results from these processes *is the most dangerous complication in diabetic hyperlipemia* The development of arteriosclerosis in cases of diabetic hyperlipemia is probably as much due to metabolic disturbances of the sugar metabolism as to the hyperlipemia as such The fats and sterols accumulating in the serum infiltrate the arteriosclerotic wall These substances are deposited in the tissue spaces and also are taken up by the phagocytes and monocytes thus producing secondary atheromatosis This mechanism is different from the origin of foam cells in essential xanthomatosis of the familial hypercholesteremic type (see section on Relation of Hypercholesteremic Xanthomatosis to Atheromatosis and Arteriosclerosis (Atherosclerosis)) It would however be erroneous to suggest that the mechanism of *atheromatosis in pathological hyperlipemia and hyper* cholesteremia can also be applied in general for the etiology of arteriosclerosis

It should be noted that the hyperlipemia never causes symptoms of embolism in the lungs and brains even if at autopsy the capillaries appear to be filled with lipemic blood * The serum in hyperlipemia in severe diabetes is not transparent and has a creamy appearance in severe cases The analysis of the serum for neutral fat and cholesterol shows an enormous increase of neutral fat and considerable increase of cholesterols The increase of neutral fat prevails

Blood—The sugar content of the serum in cases of diabetic hyperlipemia is influenced by insulin in just the same *manner that it is in cases* of simple diabetes

Clinical Course

Patients with severe diabetes and hyperlipemia with eruptive xan thoma react favorably to insulin treatment The level of the blood sugar and the hyperlipemia decreases simultaneously Hyperlipemia in severe

* Duncan (4b) recently reported that the serum *after a fat meal* as well as hyperlipemic serum coagulates more easily than serum low in fat The occurrence of thrombosis in patients with hyperlipemia is not observed However a *milky serum of* a hyperlipemic patient coagulates readily in the syringe

diabetes always is symptomatic of an extreme disturbance of carbo hydrate metabolism After the diabetic disturbance is balanced with insulin and diet treatment the tendency towards hyperlipemia is inclined to reappear again as soon as the diabetic disturbance gets out of control Blood sugar as well as blood lipids must be checked at intervals in a patient to prevent the recurrence of hyperlipemia

Differential Diagnosis

Differential Diagnosis of symptomatic hyperlipemia in severe diabetes is discussed in the sections on idiopathic hyperlipemia'

Prognosis and Treatment

Formerly it was believed that patients with diabetic hyperlipemia are inclined to fall into coma and the prognosis therefore was considered unfavorable This assumption is not correct since the hyperlipemia has no relationship to the acidosis Insulin treatment, as already pointed out controls the disturbance of the carbohydrate metabolism and as soon as the carbohydrates are normally metabolised with the help of insulin the need for fat in the tissue metabolism is reduced Consequently, the transport of fat (transport hyperlipemia) from the fat depots is no longer necessary Insulin therefore, indirectly influences hyperlipemia in diabetes

Therapy should include insulin and diet treatment The diet should be low in calories just covering caloric requirements An example of such a diet relatively rich in carbohydrates, low in fats and moderate in proteins is as follows

MENU FOR DIABETIC HYPERLIPEMIA

Cho	*Pro*	*Fat*	*Total Calories*
0 gm	74 gm	-0 gm	1 84

BREAKFAST	1 orange ½ cup rolled oats 1 slice whole wheat bread 1 glass skimmed milk
MID MORNING	1 orange
LUNCH	3 leaves lettuce 1 medium tomato carrot strips whole wheat bread, 1 teaspoon butter 1 medium baked apple with meringue (1 egg white), 1 glass skimmed milk

MID AFTERNOON ½ cup grapefruit juice
DINNER ¼ lb broiled lean meat 1 medium baked potato ½ cup string beans 1 slice whole wheat bread 1 teaspoon butter ½ large baked banana

Ca P Fe and Vitamins A B C, D G are adequate in this diet

This combination of insulin and diet treatment causes the disappearance of the hyperlipemia and glycosuria In cases where the hyperlipemia and hypercholesteremia persist after insulin application chronic pancreatitis may be found in addition to the other complications (see next section in this chapter)

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2 Hyperlipemia in Chronic Pancreatitis and Eruptive Xanthoma

Introduction

Synonyms—Xanthomatosis with recurrent pancreatitis pancreatic lipemia

Definition and Historical Notes—Speck[35] described a patient with lipemia of one year's duration (total fat 17 4 gm per cent in 1864 and 0 0 gm per cent in 1865) and attacks of colicky pain He was probably the first author to describe such a clinical condition Friedreich (1876) suggested that there was a connection between alcoholic pancreatic cirrhosis (Säuferpankreas pancreas of drunkards) and the fatty liver cirrhosis of alcoholics Lissauer[27] (1912) showed that chronic pancreatitis of alcoholics was the cause of the fatty liver cirrhosis and the lipemic blood Wiesel[6] (1905) reported an increase of fat in the blood vessels in a case of hemorrhagic pancreatitis

The occurrence of chronic pancreatitis with hyperlipemia and xanthomatosis was published by Wijnhausen[37] (19 1) Marchand[30] (1915) Joel[1] (19 4) and Brunner[18] (1935) reported similar cases of acute and chronic pancreatitis Bernhard[3] described the combination of hyperlipemia together with the enlargment of the liver and attacks of colicky pain This case belongs apparently to the group of pancreatic hyperlipemia because the patient was an alcoholic Marcus[31] reported four cases of chronic pancreatitis (one of these had already been reported by Joel[5]) controlled by operation The patients had spells of abdominal pain and transitory hyperlipemia The description of case 3 by Marcus is almost identical with that of the case of recurrent pancreatitis with hyperlipemia and secondary xanthomatosis reported by Wijnhausen[37] Marcus[31] found that only 4 out of 0 cases observed with pancreatitis showed transitory hyperlipemia Recently Collett and Kennedy[1] described hyperlipemia in an eight year old boy suffering from chronic relapsing pancreatitis

Pathogenesis

Lombroso[3] and later Joel[5] suggested that the pancreas had an antilipemic as well as an antidiabetic function each of which was dependent upon a different internal secretion The carbohydrate combustion in the liver was thought to be regulated by one internal secretion insulin and the fat disintegration by another The production of the

hormone concerned with fat metabolism may be altered without a decrease in insulin production. The occurrence of pancreatic hyperlipemia with a resulting fatty liver should, therefore, be possible also without the simultaneous presence of diabetes. To prove this opinion Joel[5] reported two cases of pancreatic hyperlipemia without diabetes. An operation was performed in the case of one of the patients, and the diagnosis of acute pancreatitis was verified. Joel also cited Wijnhausen's case where the operation showed chronic pancreatitis. However, diabetes also was present in this case. Brunner[18], in confirmation of Joel's anatomical findings, reported that acute pancreatitis was demonstrated at an operation in a case of transient, severe hyperlipemia accompanying attacks of pancreatitis.

The fact that there might be a pancreatic influence upon the fat disintegration in the liver had been suggested by Naunyn[33]. He reported the occurrence of a hyperlipemia of 12.3 per cent in a dog with a spontaneous necrosis of the pancreas and diabetes. Ever since the time von Mehring and Minkowski[3] discovered that experimental diabetes can be produced after pancreas extirpation it has been known that fatty livers and hyperlipemia develop as a simultaneous result. The discovery and use of insulin by Banting and Best made it possible to keep dogs with pancreas extirpation alive for a longer period. When these animals died after two or three months the necropsy revealed fatty and cirrhotic livers. The life of these dogs was prolonged by the feeding of raw pancreas after the pancreatectomy. The occurrence of fatty livers also was prevented (Allan, Bowie and Macleod[1]).

These experiments probably encouraged Dragstedt and associates[19, 20] to prepare a pancreatic hormone to influence the fat disintegration in the liver. This substance was named lipocaic hormone. When this preparation was fed to dogs whose pancreas had been extirpated the occurrence of fatty livers was prevented in the same way as it had been formerly by the feeding of pancreas to these animals. While Best and his coworkers[4, 12] believe that pancreatic extracts are effective only because of the choline content, their opinion is not verified by the analysis of extracts which are prepared according to the method of Dragstedt. These preparations do not contain free choline.*

* G. Schmidt, Hecht, Strickler and Thannhauser (34a) demonstrated by a new method that Dragstedt's lipocaic extract did not contain free choline but considerable amounts of bound choline, i.e., bound choline present as glycerolphosphorylcholine. This substance has according to its chemical constitution the same lipotropic activity as choline and lecithin. Since this substance is present in raw pancreas, its lipotropic activity in diabetic dogs is explained.

Clinical experience in cases of acute and to some extent chronic pancreatitis as well as experiments with animals after pancreatectomy demonstrate that the pancreatic function is connected in some ways with fat metabolism in the liver. As a result of the hyperlipemia, especially in cases where the hyperlipemia is of long duration, secondary xanthomatosis may develop.

The literature contains only one case of pancreatic hyperlipemia where secondary xanthoma developed without the simultaneous occurrence of diabetes (case of Marcus[31]). It seems justifiable to question whether the disturbance of the carbohydrate metabolism is as such responsible for the occurrence of the secondary xanthoma in cases of pancreatitis. The cases of Joel, Bernhard[7] as well as the two of Marcus[31] demonstrate that hyperlipemia occurs without diabetes in acute and chronic pancreatitis. The diabetes reported in Wynhausen's[8] and Brunner's[18] cases was not severe. In the latter case it disappeared completely. The hyperlipemia, however, only leads to an eruption of secondary xanthoma, as it did in Wynhausen's case[3], if it is excessive and present over a long period of time. The appearance of the xanthomatous eruptions in the cases of Wynhausen[3] and Marcus[1] is the same as that described in diabetic hyperlipemia as well as in idiopathic hyperlipemia (see respective sections).

It therefore seems as if the above question as to whether the disturbance in the carbohydrate metabolism is primarily responsible for the hyperlipemia and secondary xanthoma in chronic pancreatitis should be reversed. The question instead should be considered from the point of view of whether the hyperlipemia and secondary xanthomatosis in cases of diabetes is provoked by the disturbance of the carbohydrate metabolism, since in some diabetic cases not only the islets of Langerhans were involved, but also the pancreas tissue as a whole showed cirrhotic changes.

The clinical findings in cases of acute and chronic pancreatitis as well as the experimental data obtained from studies on dogs by Dragstedt and his coworkers[19, 0] show that the lack of pancreatic function may be connected with the hyperlipemia which sometimes occurs in cases of acute and chronic pancreatitis.

Clinical Cases

Case XXVI.—The patient described by Joel[5] complained of a severe pain in the upper part of his abdomen four weeks after a serious accident

(choked with earth) Diarrhea and fever were simultaneously present for a few days. After this short episode he felt perfectly well. However the pains in the mid epigastric region recurred at intervals of months and sometimes even years. They were accompanied by vomiting but no fever. The pain, which later became colicky in character, was localized mostly in the upper part of the abdomen. Seven years after the onset of the colicky pain the patient's blood was found to be milky. Although his blood had been examined previously, a milky appearance had never been observed.

The appearance of the serum did not change after laparotomy. It even remained milky after he had been placed on a diet low in fats (see Table).

	Total Fat	Cholesterol
Before low fat diet	6900–8200 mgm	700–800 mgm %
After low fat diet	6000–5700	700

The hyperlipemia was due to an increase of neutral fat, as in all other cases, to more than ten times its normal value. The increase of cholesterol to fat was about one to ten.

No obstruction of the pancreatic secretion to the intestines had ever been observed in this case. The ferments of the duodenal content were found normal. The stools contained no increased fat content. The nitrogen content of the feces also was normal. There had never been any traces of even the slightest jaundice. The blood sugar was normal. The urine was sugar free. The two outstanding symptoms, the hyperlipemia and the recurrent pain in the abdomen, continued.

Case XXXII.—The patient described by Wijnhausen[37] was a thirty-five year old obese man (85 kg.). The patient stated that he had never drunk alcoholic beverages. When he was twenty-five years old he had suffered twice from severe trauma of the stomach. After the second severe blow he had been unconscious for ten minutes. The following year he noticed small firm yellowish nodules of pinhead size on his skin. Urine examination showed no sugar. The physician recognized these nodules as xanthoma. Although the urine was reexamined five times, sugar was never found. One month (34 days) after the patient had first noticed the appearance of the xanthoma 3% sugar was found in his urine. On that day the patient also complained of loss of appetite and uneasiness in his stomach. After the patient had been placed on an appropriate diet the sugar as well as the xanthoma disappeared. However, after a few days the patient again complained of severe pain which occurred in the middle line of his stomach.

The attacks began with nausea and vomiting. During these periods the sugar content of the urine as well as the size of the xanthoma increased. The patient had high fever. Peritoneal irritation also was observed. After these

attacks which lasted for two days the patient's urine became sugar free, and the xanthoma disappeared The prescribed diet was low in carbohydrates and fat

The seizures which occurred at one or two month intervals were not always accompanied by fever but usually were preceded by the two characteristic features severe pain and prostration Xanthoma also appeared on the skin a few weeks before the attacks Large reddish plaques the size of a corn developed on the toes and drained a white milky fluid Immediately before the attack the patient became tired His abdomen was distended The stools were shiny in appearance Vomitus and severe pain just below the stomach marked the height of the attack At this time large amounts of sugar were found in the urine

After three years of such intermittent attacks an operation was performed on the patient The pancreas was found swollen tense and firm Various sized nodules were interspersed in the organ The whole pancreas was adherent to a firm tissue which penetrated the gland One of the nodules which was removed and examined consisted of necrotic tissue filled with needles of fatty acids The large epithelial cells also were filled with fatty masses The necrotic areas were surrounded by a greyish red tissue containing fat cells

During the operation the pancreas was drained and the patient recovered In the seven following years he had only three similar attacks which were however milder The patient who was engaged in a very strenuous occupation was now able to be active If he adhered to the low fat diet the xanthoma of the skin (elbows dorsal part of the hands and feet and the buttocks) disappeared. The serum however always remained milky and the cholesterol was always high (49 mgm) If the patient indulged in a diet rich in fats the sugar content of the diet was found simultaneously increased

Joel as well as Brunner[18] also described the occurrence of marked hyperlipemia in cases of acute pancreatitis In these cases however the hyperlipemia was transitory and completely disappeared after the attacks of acute pancreatitis had subsided The findings in Brunner's cases were verified by an exploratory laparotomy

Clinical Features

Skin—The xanthoma which are discrete yellow nodular eruptions usually appear on the external sides of the arms elbows back and buttocks The appearance and localization of the xanthomatous eruption is the same as that found in all types of hyperlipemia This eruptive form of xanthoma which is secondary to hyperlipemia increases and

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decreases with the intensity of the hyperlipemia. Therefore in cases where the duration of the hyperlipemia is not long or the level of the hyperlipemia is very high, xanthoma do not appear on the skin.

Abdomen.—The outstanding feature, next to the hyperlipemia, is the abdominal pain which is localized mostly in the mid-abdomen and is colicky in character. Fever is simultaneously present. Distension of the abdomen and sensitivity to touch are characteristic of the peritoneal irritation. The attacks in the chronic cases may last two to three days and are followed by long pain-free periods of many months. In acute cases of pancreatitis with hyperlipemia the abdomen demonstrates all the signs of acute peritonitis.

Liver and Spleen.—These organs usually are not enlarged. However in cases of hyperlipemia of long duration the liver and spleen are increased in size.

Stools.—During the attacks the stools are light in color. They may contain pathological amounts of fat and meat fiber. The stools are not acholic. The bilirubin is not increased in the blood.

Urine.—Sugar in cases of chronic pancreatitis or pancreatic cirrhosis may be present in the urine. The amount increases and decreases with the intensity of the hyperlipemia and indicates that in these rare instances the pancreas as a whole and not only the islets is involved. There is no report of fats or sterols in the urine, even in cases where the level of both substances in the blood is very high. The amount of diastase in the urine is increased. In the future it will be valuable to follow the curve of diastase in the blood and urine with the newer methods of observation.

Serum Lipids.—Brunner's chart (Table XXI) on acute pancreatitis is especially instructive. It shows that the hyperlipemia is of longer duration than the transient diabetes. It is evidence that, while the hyperlipemia and diabetes are the result of a disturbance of the same organ, the respective conditions are produced by distinctly different functions of this organ.

During the attack 860 mgm. per cent cholesterol was found in the hyperlipemic milky serum. After the acute attack the serum remained hyperlipemic but the total cholesterol decreased to 442 mgm. per cent. Neutral fat was not determined.

The partition of blood lipids was not done in these cases because of lack of a method at this time. The high total cholesterol values found in Wijnhausen's case[17], however, indicate that in cases of hyperlipemia in acute and chronic pancreatitis the neutral fat is not so outstandingly

increased as in cases of idiopathic hyperlipemia The cholesterols also are found elevated four to six times above normal (For figures from Joel's[5] case see Case XXXI)

TABLE XXI

Name Age	Date	Cholesterol Total mgm	Cholesterol Free mgm	Cholesterol Ester mgm	Ester in Total	Fatty Acid in mgm	Fatty Acid & Cholesterol in mgm Total fat	Diastase Wohlgemuth Blood	Diastase Wohlgemuth Urine
Normal		110–150	33–45	–105	60– 0	350	500	8	64
1 I O	11/8	Lipemic Serum			—	—	—	31	8000
35 J	12/8	1040	54)	500	50	3440	4480	96	2048
	13/8	—	—	—	—	—	4580	32	768
	14/8	676	318	358	53	2474	3150	16	51
	15/8	585	258	3 ,	56	2145	2730	16	132
	16/8	—	—	—	—	—	—	8	96
	17/8	415	168	4	59	1335	1750	8	48
	0/8	372	139	33	6	898	12 0	12	64
	22/8	353	119	34	66	74	1100	—	128
	24/8	—	—	—	—	—	—	16	128
	2 /8	400	1)	2 1	68	860	1260	8	64
	/9	245	81	164	6	910	1155	8	3
	16/9	70	80	190	0	710	980	—	32
2 S R	4/2	172	54	118	69	368	540	56	6000
45 J	5/2	—	—	—	—	—	—	32	8000
	6/	140	5	88	63	311	451	1	10 4
	/2	—	—	—	—	—	—	4	1 8
3 T I	5/	264	87	17	(	501	765	—	512
58 J	6/2	—	—	—	—	—	—	96	2048
	8/2	34	75	159	68	4 5	657	—	9
	16/	201	64	13	63	3 9	530	—	64
4 B J	30/3	127	5	70	55	493	6 0	32	000
69 J	3/4	125	47	8	65	387	51	1	64
	29/4	95	34	61	64	4 6	5 1	—	)(

Differential Diagnosis

TABLE XXI (cont)

Sugar		N P N mgm in Blood	Bilirubin mgm in Blood	Acetone mgm in Blood	Leukocytes	B S R	Insulin Units	Diet		
mgm Blood	mgm Urine							P	CHO	FAT
100	0	30–40	0 8	Trace	6–8000	10	—	—	—	—
—	3 2	46	—	Trace	15 500	15	10	—	70	—
—	4 2	56	—	8	10 900	—	60	—	100	—
192	4 3	49	0 78	16	13 200	32	60	40	100	50
218	4 3	42	—	16	9 700	—	60	50	150	50
165	5 2	42	0 78	8	8 700	40	40	50	150	50
—	4 9	—	—	16	14 000	—	60	50	150	50
119	3 0	31	0 69	8	12 200	40	80	50	150	50
192	3 3	—	0 82	4	11 000	45	80	50	150	50
—	3 3	—	—	Trace	—	—	80	50	150	50
53	0 4	25	0 33	0	14 100	38	80	50	150	50
53	0	28	0 36	Traces	—	20	60	70	120	70
108	0	—	—		7 800	27	30	70	120	70
130	0	—	—	0	—	4	—	—	—	—
135	0	45	0 88	12	11 600	35	—	—	100	—
124	0 8	31	1 1	12	—	—	—	—	100	—
121	0	32	1 0	0	—	—	—	—	100	—
120	0 5	34	1 2	1	7 800	56	—	low	250	low
—	0	67	—	Trace	18 300	28	—	—	100	—
147	0	—	2 2		13 300	—	—	—	100	—
215	0	39	1 7		10 000	30	—	—	100	—
126	0	34	0 64		13 800	60	—	low	ca 250	low
108	0	32	1 1	0	13 600	27	—	—	100	—
92	0 9	22	0 58	Traces	9 100	—	—	40	100	50
104	0	25	0 72	0	9 800	54	—	low	250	low

In chronic pancreatitis where hyperlipemia with or without secondary eruptive xanthoma is present simultaneously with glycosuria, the question to be decided is whether the underlying cause of the disease is a simple diabetes mellitus which involves only the functions of Langerhans islets or an involvement of the total pancreas as a result of acute

or chronic inflammation The differential diagnosis may be difficult if only hyperlipemia and glycosuria are found and the previous attacks of abdominal pain were not evaluated as attacks of pancreatic involvement A past history of abdominal attacks may be reported also in gall bladder disease with diabetes Jaundice occurs in these cases but hyperlipemia is rarely observed

Hyperlipemia in chronic pancreatitis is a rare occurrence The abdominal attacks with fever are the decisive symptoms for distinguishing hyperlipemia in chronic pancreatitis from diabetic hyperlipemia

The differential diagnosis between hyperlipemia due to chronic pancreatitis and idiopathic hyperlipemia with splenomegaly may present some difficulties because the occurrence of abdominal attacks with fever is also reported in the cases of familial idiopathic hyperlipemia described by Opitz[31] and Holt[4] The decisive factor in these cases is diastase determination of the urine during the period of the patient s attack An increase of diastase was not found in the patients urine by either Opitz or Holt

In the case of idiopathic hyperlipemia with secondary xanthomatosis described by Goodman and associates[23] an increase of diastase was not found in the patient s urine The child however did not have abdominal attacks The autopsy also did not reveal pancreatitis It should be emphasized that the diastase is only found increased in the urine shortly after the occurrence of pancreatic attacks Determinations made in the intervals between the attacks are not valid for diagnostic purposes

The differential diagnosis of hyperlipemia in chronic pancreatitis and von Gierke s disease (glycogen storage disease) which occurs with severe hyperlipemia may not be difficult Children with von Gierke s disease show large livers The spleen is not enlarged at all However the most important point for the differential diagnosis of both diseases is the fact that in von Gierke s disease the blood sugar is low normal or abnormally low at the onset of the hypoglycemic spell In chronic or acute pancreatitis the blood sugar is elevated

Hyperlipemia also is found sometimes in Niemann Pick s disease These cases show a slight increase in total cholesterol and a marked increase in neutral fat in the last phase of the disease Niemann Pick s disease presents an entirely different clinical picture It is a rapidly progressing disease which occurs mainly in infants during the first two years of their life (see a later part of this chapter) Hyperlipemia is never found in Gaucher s disease

During the first stages of alcoholism large fatty livers due to fat

infiltration are observed Simultaneous recurring hyperlipemia may be the result of acute or chronic pancreatic damage The atrophic form of liver cirrhosis may develop many years after the first damage of the liver by fat infiltration The occurrence of hyperlipemia in cases of liver cirrhosis indicates mostly a simultaneous involvement of the pancreas Short attacks of abdominal pain pseudo gallstone attacks as well as short spells of fever are observed in cases of fatty cirrhosis of the liver These abdominal spells are similar and probably of the same etiology as those occurring in cases of chronic pancreatitis These patients may also show slight hypercholesteremia and transient hyperlipemia

Cirrhosis of the pancreas and cirrhosis of the liver may occur simultaneously in hemochromatosis[181] Deposition of hemosiderin (iron) results in cirrhotic changes Slight diabetes and hyperlipemia may be present as a consequence of cirrhosis and hemosiderosis of the pancreas The author has observed a patient suffering from hemochromatosis and slight diabetes mellitus who developed hyperlipemia and xanthelasma The diabetes was controlled by diet but the hemochromatosis, hypercholesteremia and xanthelasma persisted

Prognosis and Treatment

The prognosis in cases of hyperlipemia and eruptive xanthoma in chronic pancreatitis depends upon the degree of the involvement of the pancreas The few patients whose cases have been reported did not die while under observation

Despite the severe transient hyperlipemia the occurrence of the eruptive form of xanthoma in acute pancreatitis has not been reported The disappearance of the hyperlipemia in the first days of the disease shows that this feature may be of prognostic value in cases of acute pancreatitis

As in all other conditions of symptomatic or idiopathic hyperlipemia the diet must be low in fats and animal cholesterols Since the external secretion of the pancreas is not involved in cases of chronic pancreatitis the amount of meat does not have to be considerably decreased

Insulin must be applied in all instances where glycosuria is present Although the diabetes disappears after insulin treatment, the hyperlipemia remains stationary Wijnhausen[37] reported that after an operation was performed the attacks of recurrent pancreatic pains were less severe and that the patient was able to carry on his profession as a lawyer An

operation was also performed on Marcus[31] patients. The first case recovered but had an attack the following year. The second had attacks of pain and hyperlipemia immediately after the operation. The third patient, whose symptoms of skin xanthoma were similar to those of the patient reported by Wijnhausen[37], died after the operation.

Patients suffering from acute pancreatitis formerly were operated upon. A drain was placed in the pancreas. However, the consensus of opinion today is to refrain from surgery in cases of acute and chronic pancreatitis. It is believed that by symptomatic treatment the patients have a better chance of surviving a peripheral vascular collapse, which may accompany the attacks of acute as well as of chronic pancreatitis.

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June 1 1949

3 Hyperlipemia in Glycogen Storage Disease (von Gierke's Disease) and Eruptive Xanthoma

In the article 'Hepato nephromegalia glycogenica' von Gierke[11] (1929) described the autopsy of a child with large liver and kidneys Chemical examination by Schonheimer[25] showed that the enlargement of these organs was partly due to an accumulation of glycogen This disease has since been known as glycogen storage disease (von Gierke's disease) See also Vol V, Chapt XLIII-A for another description of von Gierke's glycogen disease

Wagner and Parnas[8] in 1921 had already described a similar case which showed relationship to diabetes mellitus Snapper and van Creveld[6] reported the case of a child with hypoglycemia and acetonemia This condition was recognized later as von Gierke's disease The recent literature contains a number of descriptions of glycogen storage disease (for literature up to 1939 see van Creveld[7])

The high fat content of the liver together with the accumulation of glycogen had been noticed in the case described by von Gierke A high fat content was also reported by van Creveld as well as by many other investigators including Putschar[4], Kimmelstiel[17], Antopol Heilbrunn and Tuchman[1] Humphreys and Kato[16], H H Mason and D H Andersen[19] The study on the lipid factor in glycogen storage disease by Kraloower[11] directed attention to the large amount of fat in the liver and kidneys Beumer and Loeschke[4] (1933) were the first to observe an increase of cholesterol and hyperlipemia in children with this disease after extensive fat meals Beumer[3] (1937) was also the first to report that hyperlipemia in glycogen storage disease may lead to secondary xanthoma of the skin

Morbid Anatomy

An enormous enlargement of the liver without an enlargement of the spleen is the characteristic picture of von Gierke's disease When the abdomen of a child with von Gierke's disease is opened (Fig 59) the entire abdomen is filled out with the liver which occupies both upper quadrants and reaches the iliac fossa on the right The spleen on the other hand is not visible at all because it is not enlarged

The liver may be yellowish brown or yellowish white like an intensive fatty liver Microscopic examination with Best's carmine staining

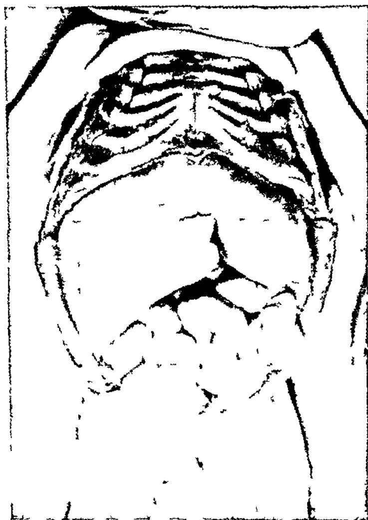


Fig 59 Von Gierke's Disease Gross anatomy of the abdomen Note the enormous fatty liver which occupies the whole abdomen No spleen is visible Compare with Niemann Pick's disease where liver and spleen fill out the whole abdomen (see Fig 115) Compare with Gaucher's disease where the spleen is the predominant organ (see Fig 97) *Through the courtesy of Dr Sidney Farber Pathological Department of the Children's Hospital Boston*

(Fig 60) reveals that the liver is filled with granules of glycogen Sudan III staining (Fig 61) also shows a great amount of fat The glycogen is found in the protoplasm of all the epithelial liver cells which are distended and appear according to Putschar[4], as large and sharply defined as plant cells' The Kupffer star cells and the endothelial cells in the liver however do not contain any glycogen

Large amounts of glycogen and fat are present in all the organs (Figs 62 and 63) kidney, heart, muscles and brain These deposits cause an enormous enlargement of these organs, especially the kidneys Chemical analysis carried out in three cases by Thannhauser and Reinstein reveal the following figures for tissue analyses (Tables XXII, XXIII and XXIV)

TABLE XXII

LIVER	I mgm %	II mgm %	III mgm %	IV mgm %	Normal mgm
Total cholesterol	0 49	0 23	1 64	0 83	0 93
Free cholesterol	0 [illegible]	0 18	—	0 17	0 34
Ester cholesterol	0 [illegible]	0 05	—	0 66	0 59
Total phospholipids	4 38	2 55	7 85	5 4[illegible]	9 80
Sphingomyelin	0 38	0 21	none	0 38	0 38
Cephalin		0 29	none	3 4[illegible]	4 6
Lecithin		[illegible] 05	7 85	1 62	4 81
Total fatty acids	34 2	5[illegible] 4	34 [illegible]	2 60	10 00
Glycogen	12 70	27 0	8 47	38 60	

These figures demonstrate an enormous amount of neutral fat besides the increased glycogen content of the liver and kidney A glycogen accumulation is not always found in the heart The fact that the gly

TABLE XXIII

KIDNEY	I mgm %	II mgm %	III mgm	IV mgm	Normal mgm %
Total cholesterol	1 04	1 19	2 73		1 13
Free cholesterol	0 66	0 57	1 06		0 68
Ester cholesterol	0 38	0 62	1 67		0 45
Total phospholipid	4 91	5 35	9 45		8 00
Sphingomyelin	0 92	0 39	0 58		0 72
Cephalin		2 40	4 78		3 26
Lecithin		2 56	4 09		5 10
Total fatty acids	12 1	4 83	13 2		—
Glycogen	31 [illegible]0	13 0		14 5	

TABLE XXIV

BRAIN	I mgm %	Normal mgm
Total cholesterol	6.04	14.9
Free cholesterol	5.00	4.6
Ester cholesterol	1.04	10.3
Total phospholipids	32.5	30.9
Sphingomyelin	6.18	5.66
Cephalin		20.4
Lecithin		4.81
Total fatty acids	1 9	
Glycogen	2.30	

SPLEEN	II mgm %	Normal mgm
Total cholesterol	2.67	0.87
Free cholesterol	1.00	0.64
Ester cholesterol	1.67	0.23
Total phospholipids	6.58	8.56
Sphingomyelin	0.91	0.86
Cephalin	1.23	4.16
Lecithin	4.44	3.54
Total fatty acids	7.25	—
Glycogen		

cogen content varies in the different organs of the same case indicates that there must be local factors causing the increase of glycogen

Van Creveld[7] obtained the following results for the glycogen content

Heart	7.92%	Muscle	9.39%
Liver	9.13%	Lung	0.034%
Spleen	1.46%	Spinal marrow	0.583%
Adrenal	1.25%	Blood (after death)	18 mgm %

Pathogenesis

The glycogen accumulation may be due to an increased formation of glycogen or to a decreased ability to split glycogen into monosaccharides Following the old conception that diastase is involved in glycogen splitting in the liver Schonheimer[2] and von Gierke[11] originally believed that the diastase in this organ was diminished It was however already stated by Schonheimer and confirmed by other investigators most recently by Thannhauser Sorkin and Boncoddo who used newer

methods that diastase is present in normal quantities in von Gierke liver Therefore, the idea that the amount of diastase present is related to von Gierke's disease had to be abandoned Schonheimer had noted already that the glycogen remained unsplit for an unlimited time after the drying of the organ In contrast glycogen in normal organs disappears almost immediately after the death of the patient

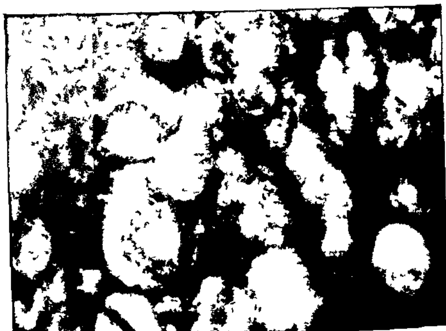


Fig. 60 Von Gierke's disease Best's carmine stain of the liver Note large amount of glycogen Empty spaces represent fat filled liver cells Histological slide through the courtesy of Dr Sidney Farber Pathological Department of the Children's Hospital Boston

It was further noted that adrenalin injections in von Gierke's disease did not produce an increase in the blood sugar Because of such factors as the low blood sugar level the hypoglycemia insulin sensitivity and acetonemia the possibility of hyperinsulinism was taken into consideration However the hypoglycemia observed as a result of islet cell tumors responds to adrenalin and does not show an enormous accumulation of glycogen in the liver and other organs

The function of the anterior pituitary was also taken into consideration for the etiology of the disease because the children affected exhibited retardation in growth with adipose features resembling a disturbance of the pituitary or of the third ventricle The so called ketogenic prin

ciple causes an increase of liver glycogen in animal experiments. It therefore was concluded that glycogen disease is a combination of hypo and hyper function of the pituitary. However, all the experimental data concerning the pituitary and glycogen storage principle are doubtful because they have not been duplicated by many investigators. The idea that pituitary dysfunction simultaneously produces glycogen storage and fat accumulation has not been proven at all and seems rather nebulous.

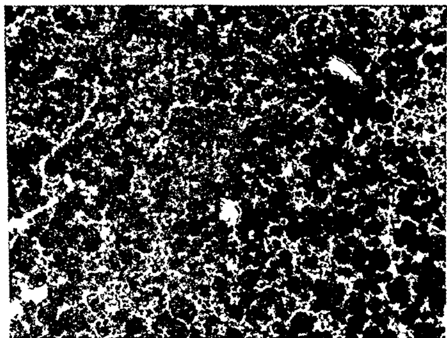


Fig. 61. Von Gierke's disease. Scharlach R stain of the liver. Note the large amounts of stainable fat. Histological slide through the courtesy of Dr. Sidney Farber, Pathological Department of the Children's Hospital, Boston.

The amylase activity is not concerned with any phase of the intermediary carbohydrate metabolism. This ferment is concerned only with the splitting of polysaccharides in the intestine. The glycogen storage disease seems to be rather the consequence of a disturbance of the intracellular carbohydrate metabolism, which is due to an enzymatic imbalance or deficiency. Since the diastase hypothesis had to be abandoned, newer experiments on glycogen synthesis and glycogen degra

dation by Cori, Cori and Schmidt[6] suggest the kind of fermentative disturbances, which may lead to an increase of glycogen within the cell.

The normal glycogen synthesis and glycogen degradation by phosphorylation is like all enzymatic processes a reversible enzymatic equilibrium expressed in the following scheme

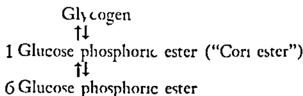


Fig. 6. Von Gierke's disease kidney. High magnification of glycogen containing tubular epithelium. Note casts of glycogen in the lumens of the tubules. Histological slide through the courtesy of Dr. Sidney Farber, Pathological Department of Children's Hospital, Boston.

In von Gierke's disease the increased glycogen formation may result from increased glycogen synthesis from 1 glucose phosphoric ester or from diminished ability to form 1 glucose phosphoric ester from gly-

cogen to inaugurate the further degradation of the glucose molecule It seems more likely that the enzymatic equilibrium is disturbed and leads to increased glycogen formation from 1 glucose phosphoric ester

Hyperlipemia is symptomatic of severe diabetes as well as of glycogen storage disease The increase of neutral fat in the serum in both instances apparently is due to the lack of metabolizable glucose in the liver In severe diabetes the glucose is present in abundant quantities but apparently not in the phosphorylated form required for further enzymatic degradation of this substance In glycogen storage disease

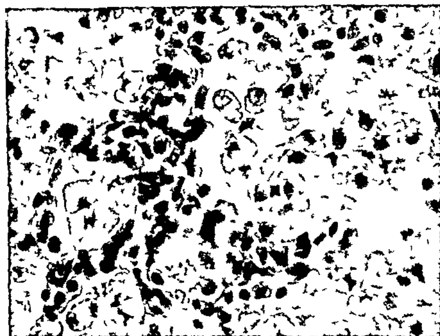


Fig 63 Von Gierke's disease Lung alveoli Note collection of large vacuolated cells which resemble those seen in Niemann Pick's disease but which do not stain selectively with Smith Dietrich stain Histological slide through the courtesy of Dr Sidney Farber Pathological Department of the Children's Hospital Boston

most of the available 1 glucose phosphoric ester is transformed to glycogen with the result that glucose phosphoric ester as well as unphosphorylated glucose is available only in diminished amounts in the liver

The effect of these two diametrically different disturbances of the enzymatic carbohydrate degradation upon the fat metabolism is how

ever, the same The lack of carbohydrate in its adequate phosphorylated form in the liver causes in both disorders mobilization of fat from the depots resulting in hyperlipemia (transport hyperlipemia)

Thannhauser, Sorkin and Boncoddo[7] demonstrated that in von Gierke's disease the alkaline phosphatase is diminished in the liver A disturbance of the alkaline phosphatase which would leave the glucose phosphate unsplit and therefore, available for glycogen resynthesis could result in an increased formation of the polysaccharide A decrease of the phosphatase activity by lowering the amount of free phosphate would also favor glycogen storage while retarding glycogenolysis The mechanism of the disease may be considered as an intracellular disturbance of the phosphorylase-phosphatase system which balances the synthesis and disintegration of glycogen

In contrast to diabetic hyperlipemia insulin does not influence the hyperlipemia in glycogen storage disease On the contrary it may increase the hyperlipemia Neither will the feeding of pancreatic substances lipocaic hormone or lipotropic substances influence the hyperlipemia of fatty liver in von Gierke's disease The hyperlipemia lessens only when nature itself corrects the fermentative imbalance of intracellular enzymes concerned with glycogen synthesis and disintegration In this respect it is of interest to note that in some cases of glycogen storage disease the condition may become less severe as the patient grows older or may even change to diabetes mellitus Von Gierke[14] in 1937 described a case where the disease progressed slowly and resulted in cirrhosis The girl lived until she was nearly fifteen years old At her death the liver contained only small islets of liver tissue and consisted mainly of connective tissue

Clinical Case

The following case reported by Beumer[3] (1937) is given as an example of von Gierke's disease with hyperlipemia because of the occurrence of secondary xanthoma

Case XXXII—R S a boy of nine years and five months whose parents grandparents and only brother were healthy When the child was six months old the mother had already noticed that his abdomen was distended Intensive dilatation of the vein of the enlarged abdomen was observed at twelve months A physician made the diagnosis of leukemia The child's condition at this time was poor He could not sit up or walk There was a marked recovery at the age of four The distention of the abdomen lessened The

child was able to walk but it was not until he was nine that he was able to move around in an almost normal way At five he had a fracture of the femur

During the following year the child manifested many peculiarities Attacks occurred early in the morning during which he whimpered continually after waking up His mind seemed dazed and his speech was faltering He complained of dragging pains which began in his feet and radiated upwards to his head Both sides were entirely flabby as if paralyzed The muscle tone on one side of his face seemed to be lessened The child understood the parents questions but was unable to reply The diagnosis of hypoglycemia and von Gierke s disease was made Sugar and chocolate were given for these attacks with immediate relief The boy later took sugar spontaneously if he felt an attack approaching By the time the child was eight years old these attacks had lessened in intensity and had become very rare Although his appetite was good he refused butter, even if his mother mixed it in his food without his knowledge

Physical examination revealed a pale obese boy with normal intelligence and alert mind His face had the appearance and expression of a well nourished baby His height was 108 cm 19 cm less than normal The development of the metacarpal bones was like that of a four year old child X ray showed that his long bones were osteoporotic His first teeth which were present were defective X ray of the skull showed a normal sella turcica The liver was enormously enlarged and extended below the umbilicus The surface of the liver was smooth The spleen was not palpable The veins of the skin of the abdomen were distended especially on both sides and above the umbilicus

Blood Chemistry —	Total cholesterol	630 mgm %
	Free cholesterol	395 36 % of total
	Cholesterol esters	235 mgm %
	Five days after cholesterol free diet	
	Total cholesterol	457 mgm %
	Three months after fat and cholesterol low diet	
	Total cholesterol	600 mgm %

Urine acetone strongly positive Urobilinogen plus

Beumer does not give any figures for neutral fat and other lipids However in accordance with the observations of other investigators and the author it may be assumed that the neutral fat was also strongly increased in the serum in this case

When the boy was three years and five months old xanthelasma appeared on the eyes and toes A large tuberous xanthoma developed on the elbow when the child was eight years old The parents stated that the xanthomatous eruptions on the toes were not constant but appeared intermittently

In this case the diagnosis of von Gierke's disease was not confirmed by necropsy because the child was still alive The diagnosis was made only on the basis of the low blood sugar, the resulting hypoglycemic attacks and hyperlipemia

Clinical Features

Physical Appearance —The infants and children have the appearance of an overnourished baby The flabby face with its baby like expression is found in older infants (Fig 64) The fat accumulation is present on the face and abdomen, while the extremities especially the lower parts lack fat The distribution of the fat is similar to that found in adults with basophilism (Cushing's syndrome) Growth is definitely retarded The children also seem awkward and clumsy

Cases of so called hepatic infantilism have a different etiology, but retardation in growth also occurs in 'hepatomegalia glycogenica' The hair usually is scanty Hypertrichosis was discovered in only one exceptional case, where a marked pigmentation was observed In all other cases the skin was found fine and marble like

Skeleton —The skeleton shows osteoporosis in most cases The bones of the skull are normal Fractures which may be observed after slight accidents, heal in normal time The calcium and phosphorus in the serum are normal The patients sometimes have a waddling gait Muscle development is poor, but neurological examination is negative An extensive enlargement of the tongue may be found sometimes

Heart —The heart is normal in many instances However, an enlarged heart has been found in several cases because of a glycogen deposit in this organ Pompe [1,3] Putschar [4], Humphreys and Kato [16] were the first to describe cases of 'cardiomegalia glycogenica' The glycogen content of the heart may vary between 4 and 33 per cent in these instances

It is very doubtful whether glycogen accumulation can be recognized in the heart during the lifetime of the patient because there are no definite symptoms The electrocardiogram is normal The so-called 'idiopathic hypertrophy of the heart' observed in children should always suggest an investigation for glycogen disease Tachypnea and dyspnea are the only symptoms clinically observed in these children Bronchial pneumonia is suspected erroneously

Liver and Spleen —The most characteristic feature of the disease is the extensive enlargement of the liver without enlargement of the spleen



Fig 64 Von Gierke's disease Child aged 2½ years Note the fat distribution on the face and neck and the resulting flabby appearance of the face The liver distends and fills out the whole abdomen The spleen is not palpable (Reproduced from Lindsay M Ross A and Wigglesworth F W., Ann Int Med., 1935 IX 274)

The liver may fill two-thirds of the abdomen causing extensive distension Von Gierke's disease can be recognized immediately at post-mortem, because there is no other disease where such a large liver with a

smooth surface and no metastasis is found Palpation of the abdomen never causes any pain An enlarged liver is already present at birth and may be seen by x-ray pictures The veins of the skin of the abdomen are not distended There are no signs of portal congestion like enlargement of the spleen and the esophageal veins or ascites In a few cases the size of the liver diminished in the patient's later years A slight transitory jaundice may be found in rare instances in infants during the first months of life

Kidney —Although the kidneys always are very large and contain considerable amounts of glycogen and fat, the function of the kidney is not impaired Only slight traces of albumin are found in the urine In anatomical preparations the tubular lumina are filled with glycogen casts Similar casts however have not been found in the urine Fliess and Bloom[10] reported a case with signs of transitory nephrosis, that is, edema and albuminuria

TABLE XXV

SERUM LIPIDS IN VON GIERKE'S DISEASE

	Serum Case 1 mgm /	Serum Case mgm /	Serum Case 3 mgm /	Normal Serum (highest figures) mgm /
Total cholesterol	53 8	412.0	160	2300
Free cholesterol	7 0	400	110.0	60.0
Ester cholesterol	60 8	172.0	1060	170.0
Total phospholipid	832 5	650.0	400.0	2 5.0
Sphingomyelin		14 3	13 7	5.0
Cephalin		62.0	none	0 30
Lecithin		573 7	386 3	150 50
Total fatty acids	4 915.0	1 8 00	1 3000	350.0
Neutral fat	4 322	1 300	995	0-150

Hyperlipemia —Hyperlipemia and a creamy serum are observed in many of the cases Neutral fat is then enormously increased Cholesterol and monoaminophosphatides also may be high The composition of the increased serum lipids is the same as in diabetic hyperlipemia (Table XXII)

Blood Sugar —Low blood sugar is a characteristic feature of the serum in von Gierke's disease Hypoglycemic attacks occur even when blood sugar is very low The blood sugar curve after the ingestion of glucose is abnormally flat Van Creveld[7] reported biphasic curves While the blood sugar remained increased longer than the normal time, the maxi

num rise was not very marked There was no glycosuria in most of the cases after sugar feeding Adrenalin injection did not always cause a rise in blood sugar It was observed in all cases that the patients are sensitive to insulin In contrast to the low blood sugar the serum contains more glycogen than is found normally

Blood Chemistry —Definite ketosis is found always in fasting blood specimens Corresponding to the acetonemia ketone bodies are found also in the urine Non protein nitrogen is normal The serum proteins have been reported as practically normal There is usually no increase of bilirubin or urobilinogen in the serum Bleeding and coagulation time is normal The number of red and white cells as well as the platelets are normal despite the tendency towards bleeding in several cases R Wagner[8] found an increase of glycogen in white blood cells a feature which may be helpful in diagnosis in some cases

Enzymes in the Serum—Several authors reported normal phosphatase in the serum Thannhauser and associates found the phosphatase sharply reduced in the liver of one of their cases Diastase is normal and low Urine diastase has been found normal and increased Van Creveld[7] found the lipolytic activity of the serum normal

Basal Metabolic Rate —The basal metabolic rate is normal or slightly increased

Diagnosis and Differential Diagnosis

The diagnosis is based on the following clinical features physical appearance enormous enlargement of the liver without enlargement of the spleen and without signs of portal congestion hypoglycemia with hypoglycemic attacks ketonuria and hyperlipemia

Two features should be investigated in making a differential diagnosis of von Gierke s disease with hyperlipemia and idiopathic hyperlipemia with hepatosplenomegaly The first feature is the size of the spleen In von Gierke s disease it is normal in idiopathic hyperlipemia it is enlarged Holt and associates[15] reported that in idiopathic familial hyperlipemia the enlargement of the liver and spleen varies with the level of the hyperlipemia In von Gierke s disease the size of the liver is enormous and does not alter The spleen is not enlarged at all

The second feature is the blood sugar In von Gierke s disease it is low normal or pathologically low with hypoglycemic attacks In idiopathic hyperlipemia with hepatosplenomegaly the blood sugar is normal or slightly increased

smooth surface and no metastasis is found Palpation of the abdomen never causes any pain An enlarged liver is already present at birth and may be seen by x-ray pictures The veins of the skin of the abdomen are not distended There are no signs of portal congestion like enlargement of the spleen and the esophageal veins or ascites In a few cases the size of the liver diminished in the patient's later years A slight transitory jaundice may be found in rare instances in infants during the first months of life

Kidney —Although the kidneys always are very large and contain considerable amounts of glycogen and fat, the function of the kidney is not impaired Only slight traces of albumin are found in the urine In anatomical preparations the tubular lumina are filled with glycogen casts Similar casts however, have not been found in the urine Fliess and Bloom[10] reported a case with signs of transitory nephrosis, that is, edema and albuminuria

TABLE XXX

SERUM LIPIDS IN VON GIERKE'S DISEASE

	Serum Case 1 mgm %	Serum Case mgm %	Serum Case 3 mgm %	Normal Serum (highest figures) mgm %
Total cholesterol	53.8	412.0	16.0	230.0
Free cholesterol	27.0	40.0	110.0	60.0
Ester cholesterol	60.8	172.0	106.0	170.0
Total phospholipid	832.5	650.0	400.0	2 5.0
Sphingomyelin		14.3	13.7	25.0
Cephalin		62.0	none	0-30
Lecithin		573.7	386.3	150- 50
Total fatty acids	4915.0	1 8 0.0	1 300.0	350.0
Neutral fat	4 322	1 300	995	0 150

Hyperlipemia —Hyperlipemia and a creamy serum are observed in many of the cases Neutral fat is then enormously increased Cholesterol and monoaminophosphatides also may be high The composition of the increased serum lipids is the same as in diabetic hyperlipemia (Table XXII)

Blood Sugar —Low blood sugar is a characteristic feature of the serum in von Gierke's disease Hypoglycemic attacks occur even when blood sugar is very low The blood sugar curve after the ingestion of glucose is abnormally flat Van Creveld[7] reported biphasic curves While the blood sugar remained increased longer than the normal time the maxi

Prognosis and Treatment

Only a few authors have reported cases where the patient recovered In most cases the disease is fatal The hyperlipemia is a rather good indicator for prognosis because the level of the hyperlipemia probably is parallel to the amount of metabolizable sugar available in the liver

At present there is no etiological therapy Different phases of the disease have to be considered in treatment If the blood sugar is low the diet should be rich in carbohydrates to counteract the hypoglycemic attacks A diet rich in carbohydrates is also necessary when vomiting is combined with the acetonuria The fear that the glycogen storage would be facilitated by such diets is unwarranted according to Van Creveld[7] If the hyperlipemia becomes an increasingly prevailing feature of the disease the diet should not be too rich in fats The diet should consist of small but frequent carbohydrate meals with sufficient proteins

Choline and other lipotropic substances are of no avail in respect to hyperlipemia and liver fat in this disorder Van Creveld believes that oral administration of choline influences the ketosis to some extent Thess and Bloom[10] reported a case where the child recovered after injection of liver extract and pitressin However it is doubtful whether the recovery was the result of the treatment and not spontaneous Other authors have not reported any effect from liver treatment or from pituitary or thyroid preparation If secondary endocrine dysfunction like lack of sexual development occurs in later stages hormone preparations *may be given symptomatically but not etiologically* X ray therapy was tried without effect

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There is some doubt as to whether the cases described by Bjorum in which fatty livers were found in four children of the same family, and the case described by Debré and Semelaigne[4] as 'stéatose hypertrophique du foie chez un nourisson' and later designated as 'hépatomégalie polycorique' belong to the group of idiopathic familial hyperlipemia or to von Gierke's disease. The name 'polycorique', which Debré himself introduced, should make it manifest that the hypertrophy of the liver in his case is caused by the combination of an increase of different reserve substances such as glycogen and fat. From this definition it can be recognized that Debré's cases of 'hepatomégalie polycorique' is identical with glycogen storage disease (von Gierke's disease) and that 'hepatomegalie polycorique' is not a separate entity.

Bjorum[3], in the paper entitled 'Occurrence of fatty livers in families' published a photograph of a seven month child whose abdomen was filled out almost entirely by the liver. The spleen was not enlarged. In the other siblings who died within their first year of life the same clinical picture was found. An intensive fatty liver was observed in all four cases at autopsy; the spleen was almost unaltered. Such extensively fatty livers with normal spleens are observed only in von Gierke's disease. In the only necropsy of a child with idiopathic hyperlipemia there was no fatty liver but only a few scattered foam cells in the organ. On the other hand the diffuse fatty degeneration of the liver, as seen in the cases of Bjorum[5], is characteristic of von Gierke's disease. It is therefore, evident that the differential diagnosis of von Gierke's disease and idiopathic familial hyperlipemia with hepatosplenomegaly is not difficult and that the two conditions may be confused only when the discussed features are disregarded.

The differential diagnosis of 'gargoylism' (Pfaundler-Hurler's syndrome) (see Vol. V, Chapt. XLIII-A of Oxford Medicine and Part V, Supplement) with hepatosplenomegaly is based on the clinical appearance of the patient as well as the absence of hyperlipemia and hypoglycemia. The same factors must be considered for essential xanthomatosis and Niemann-Pick's disease.

In cases of juvenile diabetes with enlargment of the liver the diabetic condition seems to exclude the diagnosis of glycogen storage disease. However, it should be remembered that, as in the case of Parnas and Wagner[6], there may be some unknown relationship between the two conditions.

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occurs in a certain phase of glomerulonephritis after the glomeruli have undergone severe inflammatory and degenerative changes

Genuine lipid nephrosis starts in an insidious manner The generalized hydrops which develops involves all parts of the skin face and extremities as well as the serous cavities The intensity of the hydrops may vary during the course of the disease *Corresponding to the accumulation of water in the subcutaneous tissue in the muscle tissue itself and in the serous cavities* the amount of urine voided is small usually between 200 and 600 c c The specific gravity of the urine is high

The excretion of large amounts of albumin is the most outstanding characteristic next to the edema The urine contains 1 to 5 per cent albumin equal to 10 40 grams per 24 hours In contrast to the high albumin content of the urine *the albumin content of the edema fluid is low*

At the height of the disease the serum content of the proteins may be very low sometimes 1 3 gm total proteins Partition of the proteins usually reveals that the serum albumin is reduced while the serum globulin shows almost normal values The blood pressure is normal in genuine lipid nephrosis The urine occasionally shows traces of sugar especially after the patient has been on a diet rich in carbohydrates Because the blood sugar is normal the glycosuria occasionally found in lipid nephrosis *is considered to be of renal origin renal glycosuria that is* the result of an insufficient reabsorption of sugar by the degenerated tubular epithelium The basal metabolism is below normal

The patients are pale and weak Death usually occurs from a secondary infection with pneumococcus mostly pneumococcal peritonitis Death may occur also from other infections George Fahr described an exceptional case where the patient died of uremia

The nephrotic syndrome general edema low total proteins in the serum *very high albumin excretion in the urine and doubly refractile material in the urine sediment may also occur in cases of subacute* and chronic glomerulonephritis These cases may be *distinguished from* those of genuine lipid nephrosis by such factors as the course of the disease the high blood pressure and especially the urine sediment which always contains several red and white blood cells In both instances the proteins in the serum are low and the neutral fat and cholesterol are increased The serum also has a milky appearance The name lipemic nephrosis has therefore been used to designate this condition No case

4 Hyperlipemia in Lipid Nephrosis

This section is not the place for a detailed description of the clinical picture called "genuine lipid nephrosis" which occurs mainly in children. Neither is it intended here to debate on the differentiation between "genuine lipid nephrosis" and the more frequent occurrence of the "nephrotic syndrome in chronic glomerulonephritis". Rather it is the purpose of this section to discuss the theories relating to the occurrence of hypercholesteremia and hyperlipemia which are found in both conditions in addition to the fatty degeneration of the tubular epithelium.

However at this point a summary of the anatomical and clinical observations on "lipid nephrosis" is pertinent. Friedrich von Muller[50] coined the name "nephrosis" for kidney diseases which were not the result of inflammation. Volhard and Fahr[61] and Munk[5, 51] characterized "nephrosis" as a lipid degeneration of the tubular epithelium without involvement of the glomeruli. Epstein[21] described the chemical characteristics of the nephrotic condition and introduced the term "lipid nephrosis".

In the first stage of "genuine lipid nephrosis" there may be only albuminuria (diabetes albuminuricus Lowenthal[13]). No visible anatomical changes are present. In later stages the proximal convoluted tubules are mostly affected. The fat material within the cell becomes partly double refractile. Granular casts and casts of waxy appearance are found in the lumen of the tubules and in the urine sediment. The detritus which also appears contains doubly refractile material and is easily recognized in the urine by a polaroscope.

In the classical cases of "lipid nephrosis" the glomeruli should not be affected nor should endothelial cell proliferation be found in the glomeruli. However the recent investigations of Bell[7] and Fahr[6] demonstrated that the basement membrane of the glomeruli is thickened in a late stage of "genuine lipid nephrosis". Kantrowitz and Klemperer[36] believe that the thickening of the basement membrane and even the slight swelling of the endothelial cells in the glomeruli do not indicate inflammation.

The lipids of the tubular epithelium which represent the most outstanding characteristic of nephrosis have not yet been analyzed in detail and partitioned into the different types of lipids. The only facts known are that cholesterols as well as the neutral fats are increased in the fatty cells. The same kind of fatty degeneration of the tubular epithelium

epithelium in von Gierke s disease is not accompanied by the nephrotic syndrome i e an enormous albumin excretion depletion of serum proteins and general edema

From these facts it may be concluded that an increase of cholesterol and fat in the blood even if it is accompanied by a lipid degeneration of the tubular epithelium does not produce the nephrotic syndrome The increase of cholesterol and fat in the serum is therefore not the cause of lipid nephrosis but probably is a consequence of this disturbance

The second question is whether the hyperlipemia in nephrosis is due to a disturbance of the cholesterol metabolism within the tubular cells of the kidney Such an intracellular disturbance is suggested as the etiology of hypercholesteremia in essential familial hypercholesteremic xanthomatosis However the nephrotic syndrome has never been observed in hypercholesteremic xanthomatosis even with very high serum cholesterol values In lipid nephrosis the serum is milky because of an increase of neutral fats It is therefore evident that lipid nephrosis is definitely not a part of essential xanthomatosis and has nothing else in common with the disease except the high cholesterol values of the serum

W Heymann and E Clark[23] found hyperlipemia after bilateral and unilateral nephrectomy Neutral fat cholesterol and phospholipids were increased These authors suggest that the etiology of hyperlipemia in lipid nephrosis is of renal origin and believe that the kidney itself regulates the level of the lipids in the serum The same opinion is expressed by Diaz and Castro Mendoza[1 6]

Another possibility concerning the etiology of hyperlipemia in lipid nephrosis is the connection of the nephrotic hyperlipemia with the depletion of proteins from the serum

One of the functions of the serum proteins in the blood plasma is the production of colloid osmotic pressure within the capillaries of the body The colloid osmotic pressure is effective only inside the capillaries and holds the water within the capillaries against the hydrostatic pressure blood pressure in these capillaries In contrast to the salts and water the serum proteins are supposed not to pass through the capillary walls The hydrostatic pressure therefore tends to filter off the water and salts of the plasma into the tissue as an ultra filtrate Some fluid may be filtered out from the arterial part of the capillary because the hydrostatic pressure in the arterial end of the capillary is greater than the normal colloid pressure in the capillary The fluid is reabsorbed from the tissue at the venous end of the capillary because the hydrostatic pressure is markedly

however has been observed where the hyperlipemia in nephrotic conditions is followed by secondary xanthomatosis of the skin as in other cases of hyperlipemia

The blood plasma volume in "lipid nephrosis" is reduced, according to Fahr. This finding indicates that the low proteins of the serum are not due to dilution of the serum (hydremia) but rather that the amount of the serum is diminished. The proteins are lost by the urine but not diluted in the serum

Discussion of the hyperlipemia in "lipid nephrosis" should take into consideration the following four possibilities, (1) the high cholesterol content of the serum is due to a faulty intermediary metabolism ( ) the hyperlipemia is due to a disturbance of the intracellular metabolism within the tubular cells of the kidney (3) the high cholesterol and fat content of the serum result from a depletion of proteins from the serum (4) the hyperlipemia is due to a disturbed function of the kidney which influences the inflow of fat from the depots into the serum

Bailey, Lowenthal[13] and Dewey[17] fed large amounts of cholesterol to rabbits producing hypercholesteremia in these animals. Cholesterol infiltration in the tubular epithelium and cholesterol excretion in the urine were observed in these experiments. Lowenthal[13] suggested a parallel mechanism in "lipid nephrosis". However in these cholesterol experiments the behavior of rabbits and human beings cannot be compared because as it has been pointed out already rabbits absorb freely but do not excrete animal cholesterol to any large extent. It is therefore not surprising that extensive cholesterol infiltration takes place after cholesterol feeding. In another remarkable paper on "lipid nephrosis" Lowenthal[13] discussed the mechanism of the disease from different angles. The theory that the cause of the nephrotic syndrome is a cholesterol infiltration resulting from a primary increase of cholesterol in the blood can not be considered proven

An increase of cholesterol and neutral fat may be the result of an insufficient removal of fat and cholesterol from the blood by a sluggish deposition of fat in the subcutaneous depots. The nephrotic syndrome however has not been observed in cases of idiopathic familial hyperlipemia where a sluggish deposition of lipid substances is assumed as the cause of the hyperlipemia

There may be fatty degeneration of the tubular epithelium as in cases of von Gierke's disease where extreme hyperlipemia also is present. However the hyperlipemia and fatty degeneration of the tubular

after an extensive phlebotomy A decrease of serum proteins whether it is caused by an extensive loss through glomerular filtrate as in nephrosis or through an artificial depletion by venesection, leads to an influx of fat and cholesterol from the depots (see Transport Hyperlipemia) Whether the influx is started by a loss of protein or by a mechanism which is regulated by the kidney itself remains a hypothesis despite experiments which seem to prove one or the other assumption

From figures in Table XXVI it can be seen that the blood cholesterol values rise and fall in the opposite direction from the level of the serum proteins The decrease of serum proteins is parallel with the loss of proteins in the urine It is therefore suggested that hyperlipemia in genuine lipid nephrosis as well as in symptomatic nephrosis is due to a mechanism of fat transportation which may be released by a depletion of proteins from the serum

If the last assumption is correct the hypercholesteremia and hyperlipemia in genuine lipid nephrosis' cannot be influenced by a diet low in fat and cholesterol Beumer and Gainsborough could not influence the high fat and cholesterol content in nephrotic conditions by fat free diets The author also has observed that cholesterol low diets influence the cholesterol content only during the first few days but that they do not reduce the hyperlipemia to a normal figure

Low basal metabolism and a high level of serum cholesterol in lipid nephrosis suggested a low function of the thyroid gland as a possible factor for the etiology of the syndrome Such an assumption was never verified Thyroid medication of 1 to 3 grams is however effective on the diuresis of a nephrotic patient and is useful in symptomatic treatment The goal of a sound therapy should be the increase of serum proteins A diet high in protein is not too effectual upon the level of serum proteins and will increase the level only insufficiently The effect of intravenous application of gum acacia is very questionable The infusion of human serum albumin obtained by fractionation of pooled serum by E Cohen and coworkers and applied by Janeway[314] for nephrosis seems helpful for a temporary increase of serum proteins A final evaluation of this type of treatment will have to wait until large quantities of purified human albumin are available to the medical profession

reduced, and only the colloid osmotic pressure of the proteins remains in the venous part of the capillary In fact this equilibrium between transudation and absorption in the arterial and venous part of the capillary results in a balance of fluid leaving and entering the capillary As a result the total volume of the intravascular fluid remains nearly constant

If, however the blood pressure hydrostatic pressure, and the colloid osmotic pressure in the plasma are low because of some circumstance like loss of protein the hydrostatic pressure in the venous end will then be high enough to press out the water and salt in the venous part of the capillary The fluid consequently is filtered along the whole course of the capillary from the arterial to the venous end This fluid will remain for the most part in the interstices of the connective tissue and will appear as edema

The lowering of the colloid osmotic pressure is one of the main causes of edema It is however erroneous to believe that the decrease of the colloid osmotic pressure is the "cause" of the edema in all instances In lipid nephrosis", however the depletion of proteins from the serum with its consequent reduction of the colloid osmotic pressure is parallel to the amount of edema

In experiments on dogs[4] where the blood was removed and blood corpuscles were reinjected with saline solution (plasmapheresis) the colloid osmotic pressure was reduced to about one-half and the animals developed edema in the same way that patients develop edema in nephrosis If gum acacia is injected into these animals the colloid osmotic pressure is raised the edema fluid is drawn into the capillaries again and the plasma volume is increased If gum acacia or large molecules of Congo red are injected into the vein of a nephrotic patient, they appear in large amounts in the urine indicating that the glomerular capillaries are permeable to serum proteins as well as to these two colloidal substances

The mechanism of the depletion of serum proteins seems to be the same in 'genuine lipid nephrosis' and in glomerulonephritis In the first case the glomerular tufts in Bowman's capsule become permeable through an unknown cause and without damage by inflammation In the latter case inflammation causes the permeability of the glomerular tufts to the serum proteins In both cases an increase of two or three times the normal value of neutral fat and cholesterol accompanies the loss of protein

It has also been shown by experiments with animals that the fat content of the serum increases after plasmapheresis It has been known for a long time that the fat content of the blood is markedly increased

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TABLE XXVI
SUMMARY OF CLINICAL DATA

Case No.	Dates of Trials Date	Age	Urine						B.P. Mm Hg	Edema	Blood			Renal Function	Comment
			Alb	Sp Gra	RBC	WBC	Cast	Lipoid			Chol Mgm per 100 c c	NPN Mgm per 100 c c	Albumin Globulin Fat	Dilution and Concentration test	
6	DS 12 1 35	7		1 025	1 2	3 4	0		122 68		530 0	33 4	T P 3 33 Alb 1 4? Glob 2 44	1 00 -1 030	
	2/28/36	8		1 015	2 3	0	0		105/70	0	333 3	27 7	T P 4 34 Alb 2 04 Glob 2 30	1 002-1 027	
	3/3/36	8		1 020	2 3	0	0		100 80	0	277 7	8 2	T P 5 15 Alb 2 80 Glob 2 35	1 008-1 025	
	6 23/37	9	0	1 026	1	2-3	0	0	100/60	0			T P 7 24 Alb 4 10 Glob 2 55	1 010-1 0 6	
	5 1 / 7	9	0		0	0	0	0		0					Recovered
7	H C 4 9/33	34		1 022	0	3 4	Hyalin		132/80		484 0	36 8	T P 4 32 Alb 1 80 Glob 2 [illegible]	1 006-1 028	
	6/4/33	5		1 020	0	0	0	0	130/80	0	260		T P 6 80 Alb 4 00 Glob 50		
	10 35	37	0	1 024	0	0	0	0	136/84	0					
	7 10 37	9	0		0	0	0	0		0					Recovered
8	A E 5/27/37	3		1 017	0	2 3	0		109 78		416 6	27 7	T P 4 08 Alb 3 12 Glob 1 86		
	6/1/37	3		1 035	0	2 3	many granular [illegible]		11 /84		382 8	29 7	T P 4 31 Alb 1 98 Glob 2 33		
	6/8/37	3		1 017	0	2-3	[illegible]		05/80		384 6	46 1	T P 4 50 Alb 40 Glob 2 10		Died of [illegible]

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III NORMOCHOLESTEREMIC XANTHOMATOSES

A EOSINOPHILIC XANTHOMATOUS GRANULOMA SYNONYMOUS WITH SCHÜLLER CHRISTIAN'S SYNDROME ESSENTIAL XANTHOMATOSIS OF THE NORMOCHOLESTEREMIC TYPE LIPID GRANULOMA EOSINOPHILIC GRANULOMA

Historical Notes and Definition

The historical development of the present conception and knowledge of this group as a systemic granulomatous disorder is difficult to survey since in the early literature the involvement of a single organ like the skin was not associated with an over all conception of a systemic disorder The manifestations of the skin the features first attracting the attention of the clinicians and especially the dermatologists were described as a simple skin disease Quite some time elapsed before the various types of skin xanthoma were discriminated and before it was finally recognized that xanthoma disseminata xanthoma tuberosum et plana and eruptive xanthoma (xanthoma diabeticorum) are of different etiology and represent the characteristic symptoms of entirely distinct groups of xanthomatous disorders The progress in chemical analytical methods especially cholesterol determination in the serum contributed greatly to our knowledge concerning the differentiation of skin xanthoma (Siemens[86] Rosenthal and Braunisch[77] Herman and Nathan[41] Finney Montgomery and New[illegible] and S J Thannhauser and Magendantz[9] Patients with xanthoma tuberosa et plana showed a high cholesterol level but normal or moderately increased phospholipids and neutral fat In cases with eruptive xanthoma (xanthoma diabeticorum) the serum was milky and high in neutral fat the cholesterols and phospholipids being only moderately increased The serum of patients demonstrating xanthoma disseminata in contrast to all other types of skin xanthoma, was normal in its cholesterol phospholipid and neutral fat content Even at the time when xanthoma disseminata were already discriminated from other types of skin xanthoma they were considered as a variety of xanthomatous skin disease, but their significance as a characteristic skin symptom for the clinical diagnosis of the systemic granulomatous disease under discussion was not known

Pusey and Johnstone in 1908[72] Turner Davidson and White in 1925[illegible] and Spilmann and Watrin in 1921[88] recognized the simultaneous occurrence of xanthoma disseminata of the skin together with brain

involvement (diabetes insipidus) and a peculiar type of lung fibrosis These observations however, were not properly evaluated and therefore not connected as a syndrome of uniform etiology

In the meantime Schuller (1915-16) and Christian (1919) had called attention to a clinical syndrome of defects in the membraneous bones exophthalmos and diabetes insipidus The patients described by these authors did not exhibit xanthoma disseminata of the skin For this reason the connection of the described clinical syndrome with a xanthomatous disease was not suggested until Rowland (1928-9) in his pioneer work on the histopathology of Schuller Christian s syndrome demonstrated that xanthoma cells were present in the granulomatous lesions which caused the bone lesions as well as the involvement of the brain and lung in this clinical syndrome Rowland also showed that the lesions in all organs involved in Schuller Christian s syndrome are in their histological structure identical and consist of reticulum cells and histiocytes cholesterol containing foam cells and elements of inflammation like eosinophiles round cells and polynuclear elements He considered the development of foam cells' as characteristic of the lesion as had been suggested previously by the dermatologists for xanthoma disseminata' and by Weidman and Freeman[107] who described the autopsy of a case with lesions of the skin central nervous system and other organs Chester in 1930[11] emphasized the granulomatous nature of the lesion and classified the disease as lipid granuloma' Fraser[6] in 1934-35 in a paper entitled Skeletal Lipid Granulomatosis" gave an excellent and the most complete histological description of solitary bone lesions supported by histological pictures in color He called attention to the endothelial proliferation the accumulation of eosinophilic cells and the presence of giant cells in the earlier stages of the lesion in lipoid granuloma' Horsfall and Smith[1] in the article Lipoid Granulomatosis described in 1935 a child with the complete symptom complex of the systemic variety of the disease The autopsy showed xanthoma cells in the granulomatous lesions of the bones lungs dura brain pituitary spinal cord lymph nodes and spleen According to the published photographs the patient also exhibited typical xanthoma disseminata scattered over the skin of his entire body The publication of Hand[38] in 1893, 'Polyuria and Tuberculosis must be mentioned at this point This was probably the first case of the systemic variety of this disorder reported in the literature The nature of the disease however, was not recognized by the author Hand s name is often associated with that of Schuller and

Christian in the designation of the disease while Rowland who deserves the credit for the first histological description of the lesions in the different organs is unfortunately not mentioned Thannhauser and Magendantz[9] in 1937 demonstrated on the basis of numerous clinical observations of xanthomatous diseases of heterogenous etiologies that cases of Schuller Christian s syndrome as well as of generalized lipoid granulomatosis showed normal cholesterol content of the serum in contrast to the other groups of xanthomatous diseases characterized by hypercholesteremia For this reason they used the name essential xanthomatosis of the normocholesteremic type for the monosymptomatic forms as well as for Schuller Christian s syndrome and the generalized form of lipoid granulomatosis Thannhauser and Magendantz[96] as well as Thannhauser and Reinstein[97] showed that the cholesterol content of the tissues in the xanthomatous phase of this disorder is 10 20 times higher than in normal tissue while the cholesterol level of the serum remains normal These authors therefore contended that the cholesterol accumulation in the xanthomatous cells in this syndrome is not the result of cholesterol infiltration from the blood stream but is caused by new formation of cholesterol within those cells which gradually develop into xanthoma cells (foam cells) Thannhauser and Magendantz (first edition of this chapter) first showed in their clinical material and in cases reported in the literature that various organs (skin disseminata type of xanthoma osseous system dura brain lung pleura liver spleen and lymph nodes) may be involved singly or in various combinations in the systemic disease under discussion (monosymptomatic and polysymptomatic form of the disease)

Lichtenstein and Jaffee[53] reported in 1940 in a histological study cases of solitary bone lesions (monosymptomatic form) which they designated as eosinophilic granuloma of bones These authors apparently believed at this time that this type of solitary bone granuloma was a disease not hitherto described They were apparently not familiar with the exhaustive histological description by Fraser[6] in 1934 35 of several such cases (skeletal lipoid granulomatosis)

It was not until the studies of S Farber and his coworkers[1, 214] in 194- and J L Holm G Teilum and E Christensen in 1944[44] that the designation eosinophilic granuloma was applied not only to the solitary bone lesions but also to those of Schuller Christian s syndrome as well as to the generalized lesions in other organs of the group formerly classified as lipoid granulomatosis or clinically designated as essential xanthomatosis of the normocholesteremic type Through the histo

logical studies of Holm Teilum and Christensen it was demonstrated that the natural history of such an "eosinophilic granuloma" comprises the following phases

(1) A proliferative phase in which histiocytic proliferation with accumulation of eosinophilic leucocytes is observed (see also the similar description of J Fraser 1934) In this phase there is no evidence of foam cells
(2) A granulomatous phase with increase of blood vessels and fibrils reticular cells and histiocytes eosinophiles and giant cells (Touton cells) and incipient lipoid accumulation in macrophages
(3) A xanthomatous phase with nests and isolated foam cells
(4) A fibrous stage considered as a healing phase

These four phases often show no strict demarcation during the course of the disease and their histological features may overlap considerably It is evident from the histological studies of G Teilum and coworkers as well as those of S Farber that the solitary "eosinophilic granuloma" is the monosymptomatic early stage of the systemic disease designated by Chester as well as Fraser as "lipoid granulomatosis", by Rowland as Schuller Christian's syndrome and by Thannhauser and Magendantz from the clinical point of view as "essential xanthomatosis of the normocholesteremic type"

The paper of Jaffee and Lichtenstein has caused considerable misunderstanding about the classification of the disease as seen in recent publications like the article of Weinstein and coworkers[110] The earlier authors as well as Lichtenstein and Jaffee refer to the same disease The designation of the disease under discussion as "eosinophilic granuloma" is incomplete and therefore misleading since "eosinophilic granuloma" is not a disease entity but only a phase in the histological development of a distinct clinical syndrome The xanthoma cell formation in the later phases of the lesion is as characteristic of the disease as is the reticulo-histiocytic proliferation and the accumulation of eosinophiles in the earlier phases A similar conception of the disorder also was expressed lately by Troxler and Niemitz[101]

If one does not prefer to use the older names like "Schuller Christian's syndrome" "lipid granulomatosis" or "normocholesteremic xanthomatosis" a classification should be devised referring at least to two outstanding histological phases of the granuloma namely the proliferative and histiocytic phase of the granuloma and the xanthomatous phase The designation of the localized as well as the systemic disorder as "eosinophilic xanthomatous granuloma" seems more appropriate even though it

does not embrace the characteristic and important reticulo histiocytic proliferation of the early lesions The name eosinophilic xanthomatous granuloma will be used in this section besides the older names for the disease under discussion

Pathology and Histology

The younger the individual the more rapid is the course of this systemic disease For this reason most published autopsies are those of infants Autopsies are reported by Rowland[1] Chester[2] Henschen[4] Letterer[5] Lane and Smith[7] Freud Grossman and Dragutsky Freund and Ripps and Teilum[37] The organs found involved are the skin

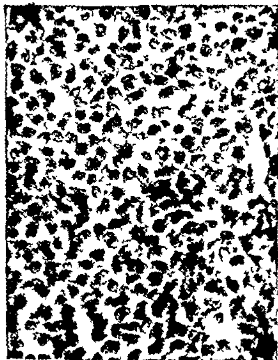


Fig 65 Tissue of reticulum cells uniformly rich in cells (Hyperplastic proliferative phase) From Holm Teilum and Christensen[44]

brain dura spinal cord osseous system lung pleura pericardium lymph nodes spleen and liver Perivascular accumulations of endothelial cells

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If one does not prefer to use the older names like 'Schuller Christian s syndrome lipid granulomatosis' or normocholesteremic xanthomatosis a classification should be devised referring at least to two outstanding histological phases of the granuloma namely the proliferative and histiocytic phase of the granuloma and the xanthomatous phase The designation of the localized as well as the systemic disorder as 'eosinophilic xanthomatous granuloma seems more appropriate, even though it

and Christensen[44] on the basis of repeated bone marrow biopsies discovered four distinct phases namely (1) the hyperplastic proliferative phase (2) the granulomatous phase, (3) the xanthomatous phase (4) the fibrous (or healing) phase

Hyperplastic-proliferative Phase—Fraser in 1935 had already described this phase very clearly attaching significance to the fact that the endothelial cells lining a capillary become swollen and detached from the vessel wall A certain number begin to migrate to the surrounding

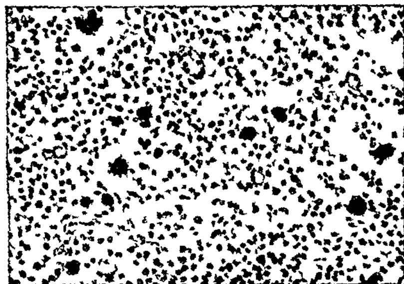


Fig. 67 Granulation tissue with numerous giant-cells of Touton type as sign of beginning lipid accumulation From H Im Teilum and Christensen[44]

tissue Some of the reticulum cells show an incipient lipoid accumulation in the cytoplasm Numerous eosinophilic leucocytes are seen in strands and clusters (Figs 65 and 66)

Granulomatous Phase—The capillary area meanwhile loses all trace of its tubular structure at the point which the original changes appeared and is occupied by several oval and fusiform cells which from their staining reaction show evidence of vascular origin Scattered among newly formed capillaries, reticulum cells and eosinophiles are several giant cells of a smaller nuclear type (Fig 67)

Xanthomatous Phase—Intracellular lipid material now becomes definitely evident in the cytoplasm of some reticulum cells which assume

but not intravascular atheromatous intima lesions like those in hypercholesteremic xanthomatosis, not infrequently are present (Fraser[8] and Teilum[93]). The organs, which may be affected singly or in numerous combinations, show the pathological findings characteristic of the disease.



Fig. 66. Eosinophile cells in clusters and reticulum cells. From Holm, Teilum and Christensen[13]

Already it had been observed by Rowland, Fraser and others that the granulomatous lesions show at different times and in various organs a changing cellular structure. Since many of the scattered lesions had a yellow color due to their content of foam cells the lesion was designated as a xanthomatous lesion, as a lipid granulomatous lesion or as cholesterol granulomatosis. In the last decade biopsies taken at different intervals have become more and more a routine procedure. The development of the cellular structure of the lesion could be studied and it was found that the lesion underwent different phases in its course. Holm, Teilum

It is understandable why a biopsy taken in the early development of the lesion does not show xanthoma cells but reticuloendothelial prolifera tion and numerous eosinophiles and is for this reason mistaken as a pure reticuloendotheliosis or as a granuloma characterized by eosinophilic proliferation It should, however be emphasized again that reticuloendothelial proliferation as well as the invasion of eosinophilic cells is as characteristic for the lesion as is xanthoma cell formation Each phase has its main cellular characteristics even though in some organs like *the osseous system the eosinophilic proliferative* phase may predominate longer than in other organs In the skin as well as in the dura and brain the xanthomatous phase develops early whereas in the lung the fibrous phase prevails very soon

At this point the possible relation of acute reticuloendotheliosis Letterer Siwe s[47] disease should be mentioned Letterer[54, 58] in 1924 had already de cribed a six month old child showing acute reticuloendotheliosis with little lipoid storage The clinical picture was characterized by fever, progressive anemia hemorrhage hepatosplenomegaly outstanding enlargement of lymph nodes and a rapidly fatal course A number of reports of similar clinical cases have appeared in the literature A rapidly fatal course and reticuloendothelial proliferation with little or no cellular lipid accumulation were the outstanding clinical and histological features[84, 44, 21, 49, 48, 34]

Schulz Wermbter and Puhl[84] were the first to express the opinion that the proliferation of reticuloendothelial cells is a primary reaction to some unknown cause and is followed by lipoid accumulation Flori and Parenti [illegible] published a case in which a biopsy demonstrated reticulosis without lipidosis but autopsy performed one year later showed typical lipid granulomatosis Freund and Ripps[29] described a similar case of lymphadenopathy with the development of bone defects seven months after the onset of the disease Typical lipid granulomatosis was found after the death of the patient about two years later On the basis of another case Wallgren[16] expressed the opinion that the absence or paucity of lipid accumulation in cases of acute reticuloendotheliosis is due to the rapidly fatal development of this type of disease The lack of development of granulomatous tissue in Letterer Siwe s reticuloendotheliosis apparently is also the result of this rapidly fatal course

The conception of four phases in eosinophilic xanthomatous granu loma (Schuller Christian s syndrome lipid granulomatosis xanthomatosis of the normocholesteremic type) is in agreement with the belief that acute reticuloendotheliosis is the earliest and most acute form of this

the shape of macrophages Finally the cytoplasm of these cells becomes 'foamy in appearance and represents cells with hardly any nuclear activity and no signs of nuclear division Sosman[89] has pointed out that the cellular arrangements in the now-called xanthomatous phase of the lesion appear to follow an interesting cycle He observed that the more mature ones of the foam or xanthoma cells are formed towards the periphery while the small mononuclear and evidently younger class of cells occupy the center of the lesion, i e the area in which the vessel, the real center of the disturbance, originally lay (Fig 68)



Fig 68 Xanthomatous tissue from the dura with typical foamy cells (Xanthomatous phase) From Holm Teilum and Christensen[44]

Fibrous Phase —The xanthoma cells and endothelial cells are replaced by fibroblast and connective tissue with the result that the lesions show an indiscriminate arrangement of fibrous tissue, fibroblasts some foam cells and also extracellular lipid deposits

These four phases often show no strict demarcation during the course of the disease and their histological features overlap considerably

the consecutive storage of this newly formed substance within the cell

Thannhauser suggested that some of the reticulum cells and histiocytes already formed in the proliferative phase of the lesion maintain the functional possibilities of embryonal reticulum cells (embryonal fat cells of Waldeyer) to form various kinds of lipids including cholesterol thus developing during the course of the lesion into xanthoma cells (foam cells) On the basis of chemical analysis of the tissue of different organs he definitely points out that the accumulation of cholesterol in these cells in the xanthomatous phase of the lesions is neither the result of cholesterol infiltration from the blood stream nor due to a cholesterol infiltration originating from a local tissue necrosis The accumulation of cholesterol in the reticulum cells and histiocytes of eosinophilic xanthomatous granuloma is therefore an intracellular process which gradually transforms these cells into xanthoma cells An intracellular metabolic imbalance of cellular enzymes concerned with cholesterol *formation but not a general disturbance of the intermediary cholesterol* metabolism results in xanthoma cell formation in this disease

It was believed that the xanthoma cell formation is connected with the etiology of the disease and that perhaps the xanthoma cell formation and its final dissolution might cause the granuloma formation This opinion must be abandoned The granulomatous lesions evolve first as reticulo histiocytic proliferation without xanthoma formation The cholesterol accumulation in some of the reticulum cells and histiocytes develops gradually and manifests itself as xanthoma cells some time after the granulomatous lesion has originated The xanthoma cell formation in eosinophilic xanthomatous granuloma resulting from an intracellular metabolic process in some reticulum cells and histiocytes of this granuloma is a characteristic feature of this disease but not the cause of the granulomatous lesion

No definite suggestion can be made concerning the etiology of eosinophilic xanthomatous granuloma (Schuller Christians syndrome) Since an infectious cause of the disease was not found a blastomatous etiology of the systemic disorder may be considered The first phase of the lesion manifesting itself as a reticuloendotheliosis may point to such an explanation

disease where only the first stage appears because infants die before the granulomatous and xanthomatous phases have had time to develop

The cases reported by Flori and Parenti as well as by Freund and Ripps lived longer and therefore showed in some areas of the involved organs the granulomatous and xanthomatous phases in their beginning Acute reticuloendotheliosis is apparently the most acute and deadly form of eosinophilic xanthomatous granuloma Its relation to Schuller Christian's syndrome is therefore, most plausible It seems however justifiable to differentiate the acute and fatal form of acute reticuloendotheliosis of infants (Letterer Siwe's disease) from the polyphasic chronic development of this syndrome (Schuller Christian's syndrome) because of the relatively benign clinical course of the latter and the multiplicity of its histological and clinical features

Etiology

The etiology of eosinophilic xanthomatous granuloma (Schuller Christian's syndrome lipid granulomatosis essential xanthomatosis of the normocholesteremic type, eosinophilic granuloma) is not known The granulomatous nature of the disease may indicate an infectious or blastomatous pathogenesis Its initial development around smaller blood vessels may be interpreted as of infectious origin but neither bacteria nor viruses have been found in cultures The patients rarely have fever and the disease does not spread with temperature elevation The accumulation of eosinophiles in the lesion prompts one to consider the lesion as an allergic manifestation but eosinophilia in the blood of these patients is not present as an outstanding symptom The clinical as well as the histological development of the lesions also contradicts the assumption of an allergic nature of its etiology

Since Rowland in his pioneer work on the histology of the disease showed the presence of numerous lipid-loaded cells (xanthoma cells foam cells) in the lesions his theory of a generalized disorder of cholesterol metabolism was favored by many authors Thannhauser and Magendantz however demonstrated that the serum lipids especially cholesterol neutral fat and phospholipids are normal in this disease The accumulation of cholesterol in the xanthoma cell in this instance is therefore not the result of a general disturbance of the intermediary cholesterol metabolism but rather of a cellular disorder which manifests itself in an increased formation of cholesterol within the cell and

the consecutive storage of this newly formed substance within the cell.

Thannhauser suggested that some of the reticulum cells and histiocytes already formed in the proliferative phase of the lesion maintain the functional possibilities of embryonal reticulum cells (embryonal fat cells of Waldeyer) to form various kinds of lipids including cholesterol thus developing during the course of the lesion into xanthoma cells (foam cells). On the basis of chemical analysis of the tissue of different organs he definitely points out that the accumulation of cholesterol in these cells in the xanthomatous phase of the lesions is neither the result of cholesterol infiltration from the blood stream nor due to a cholesterol infiltration originating from a local tissue necrosis. The accumulation of cholesterol in the reticulum cells and histiocytes of eosinophilic xanthomatous granuloma is therefore an intracellular process which gradually transforms these cells into xanthoma cells. An intracellular metabolic imbalance of cellular enzymes concerned with cholesterol formation but not a general disturbance of the intermediary cholesterol metabolism results in xanthoma cell formation in this disease.

It was believed that the xanthoma cell formation is connected with the etiology of the disease and that perhaps the xanthoma cell formation and its final dissolution might cause the granuloma formation. This opinion must be abandoned. The granulomatous lesions evolve first as reticulo histiocytic proliferation without xanthoma formation. The cholesterol accumulation in some of the reticulum cells and histiocytes develops gradually and manifests itself as xanthoma cells some time after the granulomatous lesion has originated. The xanthoma cell formation in eosinophilic xanthomatous granuloma resulting from an intracellular metabolic process in some reticulum cells and histiocytes of this granuloma is a characteristic feature of this disease but not the cause of the granulomatous lesion.

No definite suggestion can be made concerning the etiology of eosinophilic xanthomatous granuloma (Schuller Christians syndrome). Since an infectious cause of the disease was not found a blastomatous etiology of the systemic disorder may be considered. The first phase of the lesion manifesting itself as a reticuloendotheliosis may point to such an explanation.

1 Skin Manifestations of Eosinophilic Xanthomatous Granuloma (Schuller Christian Syndrome Essential Xanthomatosis of the Normocholesteremic Type, Lipid Granuloma, Eosinophilic Granuloma)

(a) Xanthoma Disseminata of the Skin

Definition and Appearance

There are three different varieties of skin xanthoma to be distinguished

(1) Xanthoma tuberosum et planum occurring in essential xanthomatosis of the hypercholesteremic type together with xanthoma of the intima of the arteries (atheroma) and of the endocardium This type is observed also in xanthomatous biliary cirrhosis (pericholangiolytic biliary cirrhosis with skin xanthoma) The serum of cases exhibiting tuberous and plain xanthoma shows high total cholesterols in the beginning of the disease normal percentage of cholesterolesters slightly increased phospholipids (lecithin) but normal or high normal neutral fat

(2) Eruptive xanthoma secondary to hyperlipemia of different etiologies These are inflammatory xanthoma which appear and disappear according to the accumulation of neutral fat in the serum (creamy serum) The cholesterol and phospholipid content of the serum is increased also but not in proportion to the enormous elevation of neutral fat (hyperlipemia)

(3) Xanthoma disseminata occurring in eosinophilic xanthomatous granuloma (Schüller Christian syndrome) either as a monosymptomatic form of this disorder or together with the involvement of the brain (diabetes insipidus) dura osseous system lung pleura liver (without jaundice) spleen lymph nodes The cholesterol as well as the phospholipid and neutral fat content of the serum of this group is normal It is possible to suggest from the type of skin xanthoma which organs may be simultaneously involved It is therefore, important to distinguish xanthoma disseminatum from both xanthoma planum et tuberosum and the eruptive variety of xanthoma

Petechiae-like lesions of the skin may occur together with xanthoma disseminata in the generalized form of eosinophilic xanthomatous granuloma (Schuller Christian s disease lipid granuloma) These petechiae like lesions show histologically only endothelial proliferation around a

capillary They may disappear completely or may develop into a typical xanthomatous lesion of xanthoma disseminata

A special variety of xanthoma disseminata occurs in infants (juvenile xanthoma) The lesion is a discrete elevated brownish or orange colored wart like lesion varying in size from a pinhead to an almond It does not occur in clusters and ridges but may be disseminated in all parts of the body as single lesions The histology shows mainly reticulum cells of endothelial origin and fibromatous tissue with interspersed rows or nests of foam cells The lesion is often classified as nevo-xantho endothelioma but there are no nevo cells The lesion may disappear as the infant grows older

In the older literature different varieties of skin xanthoma are confused and xanthoma disseminatum frequently is mistaken for the eruptive form of xanthoma (xanthoma diabeticorum)

Virchow[161] (1871) Poensgen[9–94] (1883) Fichoff[9] (1884) Koebner[56] (1888) Tschistjakoff[100] (1891) Anderson (189) Rhodes[8] (1906) all described skin xanthoma which according to the published pictures belong to the group later designated as disseminated xanthoma

The nodules of xanthoma disseminata appear mostly within the axillæ on the sides of the neck and the antecubital fossæ (Fig 69) The nodules may be isolated pedunculated or packed together In later stages they are scattered diffusely over the entire body They are slightly raised smooth patches of a lemon or chamois later maroon mahogany or dark brown color arranged somewhat in ridges or lines The patches are of irregular shape and size none of the individual lesions of which is much larger than a pinhead In such places as on the neck and abdomen the individual lesions are packed so closely together as to appear confluent However upon the stretching of the skin the patches are separated by furrows The larger patches and those of long duration are of a deeper color and well defined The smaller are of very faint lemon tint fading into the healthy skin The color is deeper in the exposed parts like the neck than in the covered parts The clusters of nodules may have a shiny metallic surface especially if their color is maroon The affected skin is elastic and pliable and can be pinched readily between the fingers In contrast to the eruptive form there is no itching of the skin to cause the patient any inconvenience

Xanthoma disseminata lesions located on the eyelids frequently do not appear as xanthoma planum (xanthelasma) but as small pinhead sized nodules which may form ridges (Fig 70) Yellow or brownish



Fig 69 Xanthoma disseminata Note the location within the axilla and around the neck The nodes are mahogany in color (case XXXVIII) Picture through the courtesy of P A O'Leary H Montgomery and A E Osterberg Mayo Clinic Rochester Minn

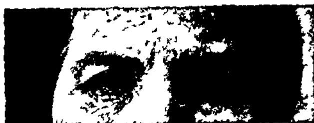


Fig 70 Xanthoma disseminatum of the eyelid (case XXXVIII) Picture through the courtesy of P A O'Leary H Montgomery and A E Osterberg Mayo Clinic Rochester Minn

plaques extend like a collar or band over the neck from which they spread slightly over the scapula and clavicle The most characteristic



Fig 71 Xanthoma disseminata within the axilla (case XXXVIII) Picture through the courtesy of P A O'Leary H Montgomery and A E Osterberg Mayo Clinic Rochester Minn



Fig 69 Xanthoma disseminata Note the location within the axilla and around the neck The nodes are mahogany in color (case XXXVII) Picture through the courtesy of P A O'Leary H Montgomery and A E Osterberg Mayo Clinic Rochester Minn

author observed a 23 year old male with an isolated xanthoma in the large bronchus. The histology of the lesion showed fibrous tissue, eosinophiles and xanthoma cells.

Histology

Several stages of development of the disseminated lesion are observed. Some of these seem to develop around a blood vessel and microscopically resemble petechiae. This petechiae type of lesion may develop into a xanthomatous lesion or may disappear completely. The fully developed xanthomatous skin lesion of the disseminata type consists of reticulum cells, eosinophilic cells and layers of xanthoma cells and granulomatous tissue (see Fig. 7). In later stages xanthoma cells and fibrous tissue are predominant. The development of the xanthomatous phase in the disseminata xanthoma of the skin occurs apparently sooner and more extensively than in visceral lesions of this type.

Chemical Analyses

Chemical analyses of the skin lesion for cholesterol shows a cholesterol content 10–[illegible]0 times that of normal skin. The cholesterol, phospholipid and neutral fat content of the serum is normal.

Familial Occurrence

Disseminated xanthoma does not occur as a familial inherited stigma in contrast to tuberous and plain xanthoma of the hypercholesteremic type of xanthomatosis (hypercholesteremic familial xanthomatosis). The family exhibiting disseminated lesions described by S. MacKenzie (1882)[63] does not belong to this group. The methods of chemical analysis of the serum were not then developed and therefore a differentiation from other types of skin xanthoma was not possible.

Clinical Course

Virchow[104], Polano[71] and Hermann and Nathan[41] described cases in which no other manifestations of essential xanthomatosis except xan

location of xanthoma disseminata is within the axillæ (Figs 69 and 71) Single nodules extend downward over the thorax and arms In contrast to the other forms of xanthoma, which may be localized on the extensor surfaces xanthoma disseminata are found in the bends of the elbows The nodules also appear on the lower lateral parts of the abdomen the base of the penis as well as the scrotum and groins Some scattered patches of xanthoma may be found in the popliteal spaces

The nodules of xanthoma disseminata are not confined to the skin but may appear also in the mucous membrane of the mouth, epiglottis larynx and bronchus as well as the cornea and sclera The appearance of the nodules in the mucous membrane of the mouth and epiglottis may



FIG 7 Histological picture of xanthoma disseminata Note large layers of foam cells (case XXXVII) Slide through the courtesy of P A O'Leary H Montgomery and A E Osterberg Mayo Clinic Rochester Minn

change later and result in scar tissue Longitudinal scars may be observed especially under the surface of the tongue If lesions are present in the mouth larynx or trachea hoarseness may be an initial symptom The

chamois color while some had a purplish hue This man was a laborer and did heavy work despite the skin tumors He was rather lethargic and did not know when the lesions first appeared There were however at the time of observation small lesions of medium and pin head size besides the large tumerous ones The patient claimed that every extensive mass developed from such a tiny lesion



Fig 73 Tumerous form of xanthoma disseminata (eosinophilic xanthomatous granuloma of skin) of the face, eyelids, neck, axilla and trunk (Case XXXIX Dr Ottenstein and Dr Obendorfer)

The patient felt otherwise healthy His physical examination was negative There was no lymph node no lung involvement The spleen and liver were not enlarged The osseous system was not involved No polyuria was noted at any time in the course of the disease Urine specific gravity 1 0 1 no sugar no albumin The serum was clear and transparent Total cho

thoma disseminata were found. A xanthomatous nodule was found in the cornea of some of the patients observed by Virchow[101] Weidman and Freeman[1] (see case XXXVII S. S.). The lesions gradually develop without any itching and without causing the patient any discomfort. If it were not for æsthetic reasons the patient would not visit a physician. In most cases, however, the lesions of xanthoma disseminatum are only the expression of other organs involved which cause symptoms of general illness. If they involve the larynx and trachea persistent hoarseness may be an initial symptom.

Clinical Cases

Cases exhibiting typical xanthoma disseminata (eosinophilic xanthomatous granuloma of the skin) are described in cases XXXVII and XXXVIII.

Atypical Clinical Cases

Case XXXIII. An Atypical Case of Disseminated Xanthoma. Diffuse Orange-yellow Flat Lesion Covering almost Entire Body

E. P., 55 years, developed diffuse yellow orange discoloration of the skin when he was 38 years of age. The yellow pigment appeared on his neck, trunk, arms and legs. An area of skin around his nipples was free. There were no definite nodular lesions nor elevation of the skin in the areas of the orange discoloration. The serum showed normal values for cholesterol ([illegible]10 mgm. per cent) and phospholipids (180 mgm. per cent). The serum was clear and transparent. There was no increase of carotene. No polyuria occurred; specific gravity of urine was 1.0[illegible]0. Histological report of skin biopsy from the Boston City Hospital: Changes consistent with xanthomatosis.

This is an atypical case of xanthoma disseminata. The author has never seen a similar case exhibiting a diffuse flat xanthomatosis. The patient died two years later of multiple myeloma. No other xanthomatous lesion involving the viscera or bones was found (Mallory Institute, Boston City Hospital).

Case XXXIV. Tumerous Form of Xanthoma Disseminata of the Skin

This 45 year old Anatolian was observed by Dr. Berta Ottenstein in Istanbul. The patient entered the hospital because a large yellow colored mass on the eyelid made it impossible for him to open his eye. He noticed similar and bigger masses on his face and especially around the neck, under the axilla, on his trunk and extremities (see Fig. 73). These were of a yellow

chamois color while some had a *purplish hue* This man was a laborer and did heavy work despite the skin tumors He was rather lethargic and did not know when the lesions first appeared There were however at the time of observation small lesions of medium and pin head size besides the large tumerous ones The patient claimed that every extensive mass developed from such a tiny lesion



Fig 73 Tumerous form of xanthoma disseminata (eosinophilic xanthomatous granuloma of skin) of the face eyelids neck axilla and trunk (Case XXXIV Dr Ottenstein and *Dr Obendorfer*)

The patient felt otherwise healthy His physical examination was negative There was no lymph node no lung involvement The spleen and liver were not enlarged The osseous system was not involved No polyuria was noted at any time in the course of the disease Urine specific gravity 1 0 1 no sugar no albumin The serum was clear and transparent Total cho

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Clinical Cases

Cases exhibiting typical xanthoma disseminata (eosinophilic xanthomatous granuloma of the skin) are described in cases XXXVII and XXXVIII

Atypical Clinical Cases

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literature which would confirm this opinion The serum analysis of cases of juvenile (infantile) xanthoma show normal figures for cholesterols phospholipids and neutral fat and are in conformity with the serum analysis of patients with skin lesions of polysymptomatic eosinophilic xanthomatous granuloma (Schuller Christian s disease lipid granuloma) There is likewise no heredity in cases of juvenile xanthoma The normal figures of the serum for all lipids exclude at once a diagnosis of familial hypercholesteremic xanthomatosis or a diagnosis of secondary xanthomatosis due to hyperlipemia

Notwithstanding the difference in visual appearance (Fig 73a and Fig 69) the histology of juvenile xanthoma and the skin lesions of eosinophilic xanthomatous granuloma (Schuller Christian s disease) have certain identical features in regard to their cellular elements In both instances the lesion begins with a proliferation of endothelial elements of blood capillaries which very soon results in an accumulation of endothelial cells reticulum cells and histiocytes in the tissue surrounding the capillaries (reticulo histiocytic proliferation so called first phase of eosinophilic xanthomatous granuloma) It is not surprising that Jacobi and Grund[1] called the lesion endothelioma cutis These authors biopsied a lesion apparently in its first phase Very soon however some reticulum cells and histiocytes develop into xanthoma cells (foam cells) while simultaneously some giant cells of the Touton type (see Fig 5 in Senear and Caro s[81] description) appear (so called third phase of eosinophilic xanthomatous granuloma) Accumulations of eosinophilic cells however in contrast to the histology of eosinophilic xanthomatous granuloma are not found in juvenile xanthoma The development of reticulum cells and histiocytes into xanthoma cells in juvenile xanthoma occurs very early and is accompanied by an accumulation of fibroblasts and a dense network of fibromatous tissue (so called fibrous healing phase of eosinophilic xanthomatous granuloma) There is no doubt that juvenile xanthoma and the skin lesion of eosinophilic xanthomatous granuloma in their histological development have the phase of reticulo-endothelial proliferation giant cell and foam cell formation as well as fibrotic changes in the end phase in common even if an accumulation of eosinophilic cells in juvenile xanthoma is not apparent The histological similarity of the lesion may suggest that juvenile xanthoma is a variety of xanthoma disseminata as observed in the polysymptomatic syndrome of eosinophilic xanthomatous granuloma (Schuller Christian s syndrome lipid granulomatosis) The designation of juvenile xanthoma as nevo xantho endothelioma is a misnomer since neither in the author s

lesterol was 190 mgm per cent cholesterol present as esters 133 mgm per cent (70 per cent of normal) free cholesterol 57 mgm per cent

Biopsies of the skin xanthoma of different sizes were examined by the late Professor S Obendorfer Istanbul (personal communication) The incipient lesion showed numerous large mononuclear cells around the capillaries no eosinophiles no foam cells The later lesion of medium size was definitely granulomatous in character Its cellular structure showed proliferation of large mononuclear cells and cells with several nuclei i e small giant cells Eosinophilic leucocytes were present in large numbers The lesions of larger size contained in addition to the mentioned cellular elements large numbers of foam cells The foam cells were mostly seen in large groups or also singly in a fine mesh work of connective tissue The large tumerous nodes were mainly formed by collagenous fibrous bonds extending in different directions in the node Few cellular elements were seen in the fibrous masses Foam cells in these fibrous masses were rare but the staining for fat demonstrated large amounts of extracellular fat mainly visible between the bonds and fibers of the masses of fibrous tissues Obendorfer stated in his summary that the histological picture of the beginning lesions is significant for a cell rich granuloma The lesion starts with an accumulation of reticulum cells and histiocytes on the outer layers of small vessels and develops in a later phase into a granulomatous lesion with eosinophiles and foam cells The lesion terminates in a diffuse fibrosis and hyalinization

Juvenile Xanthoma Its Relation to, and Variation from, the Skin Lesions of Eosinophilic Xanthomatous Granuloma

Juvenile xanthoma (nevo xantho endothelioma) is described as a discrete disseminated warthlike papular lesion which appears mostly in the first year of life[63, 81, 111] The color of the lesion varies from reddish brown to deep orange It may be as small as a pinhead or as large as an almond The lesion is a solitary papule and appears on the scalp face neck trunk buttocks and extremities In contrast to the skin lesions found in Schuller Christian's syndrome and in the generalized form of eosinophilic xanthomatous granuloma the lesions of juvenile xanthoma have no tendency to form lines and clusters It remains in all phases a solitary lesion

The parents of such infants claim that the lesions come and disappear It is the author's opinion that juvenile (infantile) skin xanthoma of the disseminated variety has a benign course It may disappear completely in later life There are however no complete follow up reports in the

is follows The picture is characterized b\ a rich peri vascular accumulation of lipoid laden histiocytes including multinucleated giant cells The \anthoma cells extend to within one cell diameter of the lateral line of re section The overlying epidermis is flattened The skin appendages in this area are encircled b\ xanthoma cells The xanthoma cells extend from the lamina propria of the epidermis through the reticular layer of the corium down into the underlying corium and along the course of the blood vessels almost as far as the subcutaneous fat There is no evidence of nevus nor of true tumor Final diagnosis juvenile \anthoma



Fig 73a Juvenile (Infantile) \anthoma See solitary lesions on chest and beneath the ear

cases nor in the cases described in the literature are characteristic nevus cells found The close relationship of juvenile xanthoma to the systemic lesions of Schuller Christian's syndrome is in some cases also clinically manifest by involvement of inner organs as in the case of Lamb and Lain[9b] It should however, be emphasized that in most of the cases described in the literature and also in the author's cases the lesions of juvenile (infantile) xanthoma are restricted to the skin and have a tendency to disappear in later life The parents of such infants who are often frightened by physicians not familiar with the benign course of juvenile xanthoma may be reasonably reassured in respect to the fate of such infants It seems however advisable to check these infants by yearly re examination and x-ray pictures of bones and lungs

In summary it may be suggested that juvenile (infantile) xanthoma is closely related to the skin lesions in eosinophilic xanthomatous granuloma (Schuller Christian's syndrome lipid granuloma) It seems to be the monosymptomatic variety of this disease in infants involving only the skin and with a good prognosis in this respect different from the prognosis of the polysymptomatic systemic disease For this reason the classification of juvenile (infantile) xanthoma should be maintained

Clinical Case

Case XXXV Case of Juvenile (Infantile) Xanthoma, Xanthoma Disseminata Type

S M a 16 month old healthy male infant height 3-¾ inches weight 23 pounds When the child was nine months old disseminated xanthoma appeared on his scalp face, right ear and both arms and legs At the time of examination the infant showed a few more orange brown disseminated lesions There were 14 normal teeth and x-ray of mandibles showed no abnormalities X ray of the lungs was negative X-ray of the osseous system revealed no lesions Blood and urine conditions were negative Specific gravity of urine was 1 030 Fasting blood sugar was 96 and 105 mgm per cent free cholesterol 38 mgm per cent cholesterol present as esters 109 mgm per cent (74 per cent of total cholesterol) Total phospholipids 159 mgm per cent total fatty acids 280 mgm per cent , neutral fat 73 mgm per cent All these values for lipids are normal

Biopsy Report Section of skin showed a sea of histiocytes many histiocytes loaded with lipid material (foam cells) There is no inflammatory component There is no eosinophilia

The biopsy of another infant whose picture is shown in Fig 733 reads

(b) PETECHIAE-LIKE LESIONS OF THE SKIN IN EOSINOPHILIC XANTHOMATOUS GRANULOMA (SCHULLER-CHRISTIAN SYNDROME)

Horsfall and Smith[45] in 1935 were the first to call attention to this type of lesions The histology of the lesions was described by Lane and Smith[51] (1939) The lesions look exactly like petechiae They are reddish purple in color usually the size of a pin head and sometimes a little larger The lesions mostly are not predominant but do develop sometimes into discrete lesions of xanthoma disseminata Usually they disappear leaving behind a little spot of brownish discoloration They are diffusely scattered over the whole body and do not ulcerate Their identity is easily confused with that of petechiae as in the case of C C (Case XLII), who had epileptic seizures from xanthomatous brain lesions When this man was observed in a field hospital, it was believed that he had epidemic meningitis because of these so-called petechiae which were later histologically recognized as lesions of eosinophilic xanthomatous granuloma (Schuller-Christian s disease)

Histology

In the early stages an accumulation of large mononuclear cells with irregularly shaped nuclei and eosin staining cytoplasm is found This group of cells lies in the connective tissue of the cutis just beneath the epidermis They are endothelial cells and seem to develop from the outer walls of the capillaries Not all capillaries are surrounded by these monocytic cells There are also a few lymphocytes and plasma cells The dominating feature at this stage is the accumulation of large reticulum cells and histiocytes apparently in connection with the capillary walls with hemorrhagic exudation in the connective tissue (see Figs 86 and 87) (B C Case XXXVI and C C Case XLII)

In later stages the mononuclear cells show a more abundant cytoplasm and take a paler stain In some areas the cytoplasm has a foamy appearance No definite foam cells or accumulation of eosinophilic leucocytes is seen in these petechiae-like lesions Such a later phase is only observed if in rare instances the petechiae-like lesions develop into a true disseminated xanthoma

Clinical Course

Petechiae like lesions and xanthoma disseminata may be observed simultaneously in the same patient Lane and Smith[51] described three

cases of children with Schuller Christian syndrome (systemic eosinophilic xanthomatous granuloma) where the petechiae like lesions were present Case C C 38 years old (Case XLII) showed petechiae-like lesions at the same time with xanthoma disseminata and eosinophilic xanthomatous lesions of brain and bones Case B C Case XXXVI had xanthoma disseminata and wide spread petechiae like lesions especially on his trunk At the beginning of the disease he had polyuria which later ceased completely The skin manifestations were the only features of the disease in later life (See Figs 74 and 75)

Case XXXVI (B C) a 45 year-old police officer observed disseminated yellowish skin lesions together with pin point purple lesions when he was 25 At this time he had polyuria and voided 3 4 liters of urine In later years the polyuria disappeared but the skin lesions spread over the face neck and trunk Axillae buttocks scrotum anus and legs were involved also but the skin lesions of both types were less than on the face and trunk (see Figs 74 and 75) The lesions disfigured the face there was no spot of unchanged skin The patient performed his full duty as a police officer and had no other complaints X rays of the osseous system were normal Specific gravity of his urine 1 010 1 0 0 Lipid analysis of serum showed total cholesterol 190 mgm per cent free cholesterol 57 mgm per cent cholesterol present as esters 133 mgm per cent (70 per cent of total cholesterol) total phospholipids 170 mgm per cent Serum was clear and transparent The patient died suddenly while on duty No autopsy was performed

Diagnosis and Differential Diagnosis of the Skin Lesions of Eosinophilic Xanthomatous Granuloma from Lipoid Proteinosis (Urbach) and from So called Eosinophilic Granuloma of the Skin

Virchow[104] who first designated as xanthoma multiplex molluscum lipoides a form of xanthoma different from that of tuberosum et planum had already pointed out that this type was pedunculated molluscum like and brown in color as shown by his colored lithograph Until the publication of papers by Polano[1] (1936) and Montgomery[66] (1937) xanthoma disseminata were confused with other varieties of xanthoma Xanthoma disseminata are however entirely different from both xanthoma planum et tuberosum and the eruptive form of xanthoma in size color and localization Xanthoma disseminata are located on the hollows of the knees and elbows but not on the extensor surfaces The color is not ochre or carrot like but lemon and in later stages dark brown mahogany or maroon The lesions sometimes have a shiny metallic surface

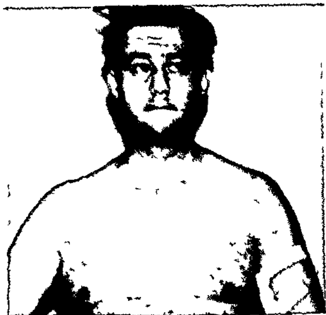


Fig 74 Xanthoma disseminata of the skin in eosinophilic xanthomatous granuloma together with petechiae like lesions (case XXXVI)



Fig 75 Petechiae like lesions over entire back (case XXXVI)

Urbach[103] and Montgomery and Havens[8] the histological structure is unquestionably different from that of xanthoma disseminata because in the latter foam cells are abundant while in the former there are no foam cells but only some extra cellular lipid deposits The fact, however, that these scarred lesions under the tongue, on the epiglottis and pharynx appeared simultaneously with xanthoma disseminatum led Thannhauser and Magendantz[96] to believe that lipoid proteinosis (Urbach) is the burned out lesions of xanthoma disseminata i e the fibrotic phase of this lesion with extracellular lipid deposits

In the recent dermatological literature skin granulomas are described with an accumulation of eosinophilic cells in a granulomatous infiltrate of the skin (Weidman[108] Lewis and Cormia[4] Lever[7], Guilchow and coworkers[314] and Vinta and Gadrat[6]) These plaque like infiltrates of the skin (cheeks axillae and thigh) are of a purplish red color at the beginning but fade out during the course of the disease leaving behind a brownish discolored scar (Lewis and Cormia) The infiltrate feels soft almost elastic to the touch (Lever) No other organs but the skin are involved The histology of the lesion exhibits reticulo-endothelial proliferation and increase of eosinophiles in the tissue In all cases arterial changes of the kind seen in inflammatory arterial diseases like vascularitis endarteritis and periarteritis with thickening of the arterial linings are observed Such a definite vascularitis is not found in the skin or visceral lesions of the eosinophilic xanthomatous granuloma

The endothelial proliferation in the first phases of eosinophilic xanthomatous granuloma seems to originate sometimes from the endothelial cells of some capillaries However it never results in a definite perivascular accumulation of pleomorphic cells and especially does not lead to an arteritis with permanent thickening of the arterial linings Clinically the distinction is even more evident The lesion is reddish brown plaque-like and may disappear as in Lewis and Cormia s case Neither the color or the shape of the lesion is similar to the skin lesions of eosinophiles xanthomatous granuloma Weidman also does not consider the so-called eosinophilic granuloma of the skin as another type of skin manifestation of eosinophilic xanthomatous granuloma (Schuller Christian syndrome) Lever, on the other hand is more inclined to believe that eosinophilic granuloma of the skin' is another sign of this disorder In the author s opinion the clinical features as well as the endaritis seen in biopsies are of great importance for the differential diagnosis of so called eosinophilic granuloma of the skin from the skin

The lesions are observed in the mucous membrane of the mouth under the surface of the tongue and may appear in the pharynx and larynx and bronchus In these places they are unlike those found in the skin and appear not as small nodular lesions but as light yellow patches of longitudinal infiltrations Sometimes no yellow color is present to give a reminder of xanthoma Because these lesions (mucous membrane mouth pharynx) are found without xanthoma disseminata in the skin Urbach[103] classified them as separate entities of xanthoma and called them "lipoid proteinosis' He also designated them as 'phosphatide lipoidosis because extra cellular lecithin is found increased in the tissue (Montgomery and Havens[6]) He distinguished two forms, nodular and hyper keratotic Urbach[103] found scars on the face, like the scars of smallpox which appear during infancy and leave these variolar scars remaining Thannhauser and Magendantz[96] preferred not to distinguish between lipoid proteinosis (Urbach) and xanthoma disseminata because both forms occur together in the cases of Pusey and Johnstone[7] Turner Davidson and White[10] and Finney Montgomery and New[73] The photographs and colored pictures of the case described by Urbach[103] are exactly like those of Turner Davidson and White[10]

The skin manifestation of 'lipoid proteinosis', described by Urbach[103] simultaneously with the lesions of the mouth and larynx, are characterized by numerous pinhead-sized lesions grouped in mulberry like warty clusters These lesions are from the point of view of size appearance localization and color (brown violet sepia) identical with the lesions first described by Virchow[104] (1871) and by other authors and classified according to Polano[71], Montgomery and Osterberg[64] as xanthoma disseminata

Basing their conception on the newer literature as well as on their histological and histochemical studies Montgomery and Havens[6] tried to reaffirm Urbach s statement that lipoid proteinosis is a separate entity and in their opinion a nevoid disturbance of lipid metabolism Montgomery and Havens[6] stressed as their main point the fact that no foam cells are found in these scar lesions but an extra-cellular deposit of phospholipids around the vessels, in the blood serum neither lecithin nor cholesterol is increased According to Montgomery and Havens[6] the lesion itself is different from that of xanthoma It is of brownish hue or sometimes colorless The fact that in the histological stain the connective elastic tissue is fused into a homogenous uniform mass may lead to confusion with hyalin deposits or amyloidosis of the skin According to

region by pressure In the third there is xanthomatous involvement of the substance of the brain itself a condition which is the most frequent cause of diabetes insipidus in normocholesteremic xanthomatosis Xanthomas may involve the pituitary the stalk and most frequently the tuber cinereum and hypothalamic region

Xanthomatous lesions of the brain exhibit eosinophiles foam cells and granulomatous tissue In lesions of long duration the foam cells subsequently may disintegrate and deposit free cholesterol which becomes visible in the spaces of brain tissue In the fibrous scars of such xanthoma of the brain xanthoma cells may be found lacking and the granulomatous scar tissue may give the impression of a fibrous tumor

In the monograph Forme Cerebrale de la Cholesterinose van Bogaert Scherer and Epstein[9] described in detail the histological changes occurring in the nervous system While this form did not involve the centers around the third ventricle or show diabetes insipidus the kind of histological changes were however similar to those described in lesions of the brain in the disease under discussion

Clinical Cases

Case XXXVII—S S* a forty two year old man (193) first seen in June 19 7 had noticed increased thirst and polyuria in November 19 , He drank about o glasses of water during the day and woke up at night because of thirst He could not remember any illness or other incident which might have caused the condition At about the same time he noticed yellowish brown elevated areas on the skin of the antecubital fossæ It seems probable that the appearance of these lesions antedated the onset of the diabetes insipidus but that they were not striking enough to attract the patient s attention for some time Similar soft tumor like nodules presently appeared in both axillæ and on the sides of the neck and smaller paler nodules under the eyes At his first visit general examination was essentially negative except for the lesions in the skin in the areas mentioned He was found to be passing not more than ooo c c of urine daily and his oral fluid intake was recorded as not more than 2 200 c.c The specific gravity of the urine varied from 1 006 to 1 012 Roentgenograms of the sella turcica were negative The blood sugar was 0 10 per cent the basal metabolic rate was normal plus 3 per cent A biopsy made from one of the nodules in the axilla revealed the typical picture of xanthoma (Fig 72)

* This case and Case XXXVIII are published by permission of P A O'Leary H Montgomery and A E Osterberg Mayo Clinic Minn

lesions of eosinophilic xanthomatous granuloma (Schuller Christian syndrome) D Lever was kind enough to give our laboratory a biopsy specimen of such a skin lesion for chemical analysis The cholesterol (0 230 mgm per cent, total cholesterol) as well as the phospholipid content (1 49 mgm per cent) (normal 0 1-1 5) was normal even low normal in contrast to the skin lesion (disseminated xanthoma) of eosinophilic xanthomatous granuloma (see S S Case XXXVII) where total cholesterol was found to be 4 55 mgm per cent

Involvement of Other Organs

Xanthoma disseminata of the skin may occur simultaneously with diabetes insipidus or other symptoms of brain involvement The lesions may be found also with diabetes insipidus, brain involvement bone xanthoma and lung involvement Despite the fact that xanthoma disseminata may be the only feature of eosinophilic xanthomatous granuloma (xanthomatosis of the normocholesteremic type) search has to be made for involvement of other organs

2 Diabetes Insipidus and Xanthoma Disseminata of the Skin

Diabetes insipidus with xanthoma disseminata was first described by Spillmann and Watrin[90] who found neither bone changes nor exophthalmos in the case reported Other authors also showed that diabetes insipidus and xanthoma disseminata may occur without lung and bone involvement

The clinical signs of diabetes insipidus are attributed to disturbed function of the posterior lobe of the pituitary gland pressure or irritation of the base of the brain (tuber cinereum) or interruption of the nervous structures connecting the pituitary stalk with centers of the third ventricle by the anatomical lesions around the third ventricle

Lesions of eosinophilic xanthomatous granuloma of the dura and brain may result in all of the three different centers of involvement In the first type the yellow rubbery xanthomatous nodules of the dura may compress the pituitary body thus causing atrophy of the stalk In the second the same kind of masses in the dura may compress the base of the brain leaving the pituitary intact but damaging the subthalamic

tive Roentgenograms of the thorax and sella turcica were negative The eyegrounds were essentially normal Blood chemistry cholesterol 167 mgm % cholesterol esters 119 mgm % total phospholipids 46 mgm % fats as fatty acids 73 mgm % Tissue analysis one nodule was excised and the analysis of the dry tissue was as follows total cholesterol 4 55 mgm % cholesterol esters 3 66 mgm % fatty acids 3 64 mgm %

Case XXXVIII—Mrs H A married forty-eight years old was examined at the Mayo Clinic in June 1936 because of polydipsia In June 1935 she noticed small red and yellow papules under the arms and in the groin These increased in spite of roentgen ray treatment In March 1936 many lesions developed on the eyelids (Fig [illegible]) Six months after the first onset of the cutaneous lesions (January 1936) she developed symptoms of diabetes insipidus including marked polyuria and an output of eight gallons of urine daily The diabetes insipidus was controlled fairly well by the use of pituitrin and amidopyrine Examination of the skin revealed red brown nodules from the size of a pea to a pin There were also lesions in the mouth The hemoglobin was 13 4 grams per 100 c c of blood the erythrocytes numbered 4.9 million per cu mm, and leucocytes numbered 10 600 The differential count was as follows lymphocytes 31 0 monocytes 4.5 neutrophiles 60 5 eosinophiles [illegible] and basophiles 1 5 per cent The flocculation test for syphilis was negative The urine showed specific gravity of 1 009 Roentgen ray of the chest was negative Roentgen ray of the skull including the sella showed a benign frontal hyperotosis

In February 1937 the skin lesions had become much more numerous in the axilla (Fig 71) and groin There was also a marked diffuse reddish infiltration of the face over the area usually involved by acne rosacea but made up entirely of miliary xanthoma There was involvement of the eyelids (Fig 70) over the axillæ lower portions of the breasts abdomen labia and inner surfaces of the thighs and a few lesions were present in the cubital fossæ all of this in spite of the fact that the diabetes insipidus appeared to be quite well controlled

At this time the erythrocytes were 4 6 million per cu mm and the leucocytes 8 700 The urine showed a specific gravity of 1 007 There were xanthoma involving both cheeks and the floor of the mouth There were some suspicious areas on the margins of the tongue, both arytenoid regions showed definite yellowish nodular areas For serum analyses see Table XXVII

When the patient was examined May 10 1937 she had been feeling well and had been having very little trouble with thirst or polyuria She had been taking three amidopyrine tablets at night and three injections of pituitrin a week All the skin lesions were somewhat more extensive than in February The bilirubin was 1 0 mgm % reaction indirect The liver no longer was palpable

The patient returned to the Mayo Clinic in January 193 showing marked increase in the number and extent of xanthomatous lesions as compared with the status shown by photographs at the time of his previous visit The progression had been so gradual however that he could not state whether they were still increasing or were stationary About two years before this last visit xanthomatous nodules had appeared around the anus and had been excised because of itching They had recurred in an area of larger radius and the itching associated with them formed his chief complaint His thirst and polyuria were of less degree he thought than on his former visit He had tried hypodermic injections of solution of pituitary in 19 7 and had found that they controlled his thirst but he had not experienced sufficient discomfort to continue the use of the drug

Examination disclosed large areas of soft confluent bronze colored nodules in each axilla (Fig 69) There were smaller areas in each antecubital fossa where the nodules were pinkish brown Some of these tumors were slightly pedunculated and as large as by 1 by 1 cm There were numerous smaller flat nodules on the neck face groins and sides of the abdomen Around the anus for a radius of from 6 to 7 cm the skin appeared smooth gray and thick perhaps owing in part to the previous excision of nodules At the periphery of this area were soft sessile pinkish tumors like those in the hollows of the elbows A continuous ridge of nodules ran along the median raphe to the scrotum where it ended in several nodular enlargements

Again it was interesting to note that there were no lesions on the elbows knees or surfaces subject to trauma In the mucous membrane of the mouth there appeared five yellowish areas one on the left margin of the tongue one in each cheek one over the left lower jaw and one in the uvula There was no involvement or scarring of the posterior pharyngeal wall There were eight areas visible in the larynx and upper part of the trachea where the mucous membrane similarly was involved As far as one could see down the trachea the same condition was present There was no scarring in the larynx or trachea and no embarrassment of respiration On the upper part of each cornea covering the upper margin of the iris was a yellow slightly elevated mass resembling so closely some of the other nodules particularly those in the mouth that there seemed no reasonable doubt of their identical nature Biopsy was made from a nodule on the arm and again revealed typical xanthoma not differing essentially from the picture seen five years before in tissue from the same patient

General examination was essentially negative except for the lesions described The output of urine was between two and three liters daily the specific gravity was 1 010 urinalysis was negative The concentration of hemoglobin was 10 8 gm (64 per cent) erythrocytes numbered 3 5 million per cu mm and leucocytes 11 700 Serologic tests for syphilis were nega

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TABLE XXVII

	6/6/36	7/9/36	2/6/37	3/7/37	5/12/37
Total cholesterol	214 mgm %	235 mgm %	349 mgm %	297 mgm %	208 mgm %
Total fat as fatty acids	30	250	273	231	290
Total phospholipids	305	269	514	405 "	260
Cholesterol esters					134
Free cholesterol					74 "

Clinical Features

Skin.—Xanthoma disseminata were present and had the appearance described in the previous section.

Diabetes Insipidus.—These cases cannot quite correctly be designated as severe diabetes insipidus because of the generally accepted fact that patients with the severe form of diabetes insipidus are unable to produce a urine with a concentration higher than 1.003. The cases reported in the literature as well as the two described above had a specific gravity of about 1.010 despite the polyuria. In all these cases no analysis was made of the sodium chloride content of the serum or the urine. However, there is not the slightest doubt that the polyuria belongs to the group of diabetes insipidus and not to the so-called nervous polydipsia because, as it has been stated already, anatomical lesions are found in the pituitary stalks or hypothalamic region in all these cases. The fact that an anatomical substratum was verified should lead to a reconsideration and abandonment of the term "nervous polydipsia" for these patients despite the fact that urine concentration as high as 1.010 was observed. Patients with diabetes insipidus as a symptom of xanthomatosis of the brain and dura benefit from the usual therapy: injection of posterior pituitary lobe extract or sniffing of posterior pituitary powder.

Blood chemistry.—Total cholesterol as well as other lipids in the serum are normal.

Differential Diagnosis

In all cases of diabetes insipidus, especially in young people, search should be made for xanthoma of the skin and bones. Most cases of

diabetes insipidus do not belong to the group of eosinophilic xanthomatous granuloma. Some cases however of diabetes insipidus are not diagnosed as xanthomatous brain lesions, because it is not generally known that diabetes insipidus may occur without changes in the bones of the skull. Unfortunately examination of the blood for cholesterol does not help in making a diagnosis because in these cases the cholesterol is found normal. The only hint of diagnostic value may be the simultaneous occurrence of xanthoma disseminata of the skin.

3. Eosinophilic Xanthomatous Granuloma of the Bone (Eosinophilic Granuloma of Bone. Osseous Xanthoma)

Definition

In the first edition of this section it was stated that osseous xanthoma is a monosymptomatic form of the disease under discussion has been described only in a few instances.[5] Meanwhile numerous cases have been reported.[32, 48, 50] Lichtenstein and Jaffe called attention to this type of bone lesion in their paper "Eosinophilic Granuloma of Bones" with the effect that roentgenologists became conscious of the bone lesions.[1, 40, 46, 15, 36] The histological studies of S. Farber and coworkers as well as Holm, Teilum and Christensen demonstrated that these solitary bone lesions designated as eosinophilic granuloma of bones are identical with those found in different visceral organs in the Schuller-Christian syndrome. The accumulation of eosinophiles after the reticulo-endothelial proliferative phase is only another phase in the course of the lesions (for discussion see pathology and histology in this section). The xanthomatous phase follows the stages of reticulo-endothelial and eosinophilic proliferation. Since the xanthomatous phase is as characteristic a feature as the reticulo-endothelial and eosinophilic phases, it seems more appropriate in order to avoid confusion in the nomenclature to designate the histological lesion as eosinophilic xanthomatous granuloma of bone and to consider cases with isolated bone lesions as monosymptomatic types of Schuller-Christian syndrome (essential xanthomatosis of the normocholesteremic type).

Clinical Cases

Case XXXVIII.—S. S.,* a four year old girl who began to limp, had no family history of bone diseases. Roentgen ray examination by her physician revealed multiple bone lesions of the hyperparathyroid type.

* The patient was sent to Dr. Fuller Albright of the Massachusetts General Hospital, to whom the author is indebted for the privilege of seeing the child.

Her appearance was that of a normal four-year old child There were no signs of xanthomatosis of the skin The skull formation was normal There was no exophthalmos or diabetes insipidus There was a sharp con



Fig 76 Roentgen ray of the skull shows osteolytic xanthomatous bone lesion (case XXXVIII) Picture through the courtesy of Dr Fuller Albright

trast between the normal appearance of the child and the findings revealed by roentgen-ray examination of the bones The following report was made in April 1936 The skull (Fig 76) pelvis (Fig 77) femora tibiæ left scapula left ulna right radius both humeri the right ninth and tenth and the left sixth ribs show smooth sharply defined punched out areas of bone destruction The most extensive changes are seen in the upper ends of the

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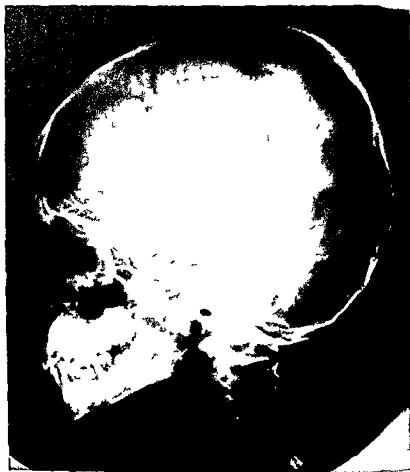


Fig 76 Roentgen ray of the skull shows osteolytic xanthomatous bone lesions (case XXXVIII) Picture through the courtesy of Dr Fuller Albright

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left femur and in the wings of the ilia The head of the left femur is partially destroyed and the shaft of the left femur in the region of the trochanter and neck shows multiple vacuolated areas of diminished density with smooth sharp dense margins The lower end of the left femur and the upper end of the tibiae show irregular calcium deposits in lesions which may have been areas of destruction There is a lesion in the left humerus at the junction of the middle and lower third which is quite unlike all the other lesions described It is characterized by moth eaten bone destruction and extensive periosteal proliferation along about 3 inches of the shaft on the lateral surface No fracture is seen at this point and the soft tissues are



Fig 77 Roentgen ray of the pelvis with xanthomatous osteolytic bone lesions (case XXXVIII) Picture through the courtesy of Dr Fuller Albright

normal The bones show a slight degree of osteoporosis and their density is within normal limits except in the region of the lesions described

Comparison of these films with those taken in May 1934 shows definite *increase in the number and size of the osteolytic lesions* There has been apparently complete healing in a lesion at the upper end of the left humerus since 1934 It is probable that the lesions in the lower ends of the femora and tibiae likewise are healed but no previous films are available for comparison

Tissue was obtained by biopsy from the bone marrow of the scapula and gave the following results by chemical analysis

Tissue (dried)	Cholesterol content	07 mgm %
	Serum calcium	10 6 "
	Serum phosphorus	5 6 "
	Serum protein	6 4 gm %
	Serum phosphatase	6 5 units
Serum lipids	Total cholesterol	150 mgm %
	Free cholesterol	40 "
	Cholesterol esters	110 "

The following histological findings (Fig 78) were reported by Dr Granville Bennet of the Harvard Medical School The tissue is very vascular being traversed by numerous thin-walled capillaries In most areas there is little supporting tissue between capillaries However in a few areas there are larger amounts of connective tissue that indicate slight fibrosis of the bone marrow The cytological picture of the tissue is greatly varied Large collections of bone marrow cells are observed in some areas In other areas the hematopoietic cells are scattered in between good sized collections of large mononuclear cells which appear definitely abnormal These cells vary markedly in size and shape The majority are oval or round The cytoplasm usually is well stained with eosin dye In many of the cells however the cytoplasm is finely vacuolated or contains brownish pigment or in some instances it contains both pigment and finely divided vacuoles The nuclei of the majority of these cells are oval or kidney shaped Certain areas show marked accumulations of these cells However in the majority of fields such cells are scattered in small groups through the marrow tissue

Case XXXIX — This 5 year old man M I was first seen in 194 by Dr H Brugsch in the outpatient department of the Boston Dispensary and his case reported in the Bulletin of the New England Medical Center[4] He complained about fatigue His parents told him he had always had thin bones and suspected something wrong with his skeletal system However he participated in all kinds of athletic activities There had been no fractures no bone pain no polyuria no family history of any importance The reason for his examination at this time was his rejection by the army for a heart murmur One year later he was accepted by the army He did not mention his bone condition to the examining physician of the draft board

Physical Examination — The patient was a healthy looking thin boned man 5 feet 5½ inches high weighing 1-9 pounds There was no deformity Skin and mucous membranes were pale no skin lesions were found No exophthalmos was present Teeth were normally developed There was no adenopathy Lungs showed vesicular breathing no râles no dullness X-ray of the lungs gave normal findings Heart was normal in size with a

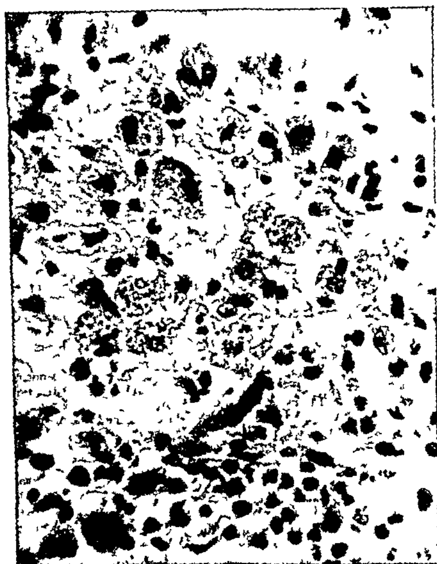


Fig 78 Histologic picture of a xanthomatous nodule of the bone marrow (case XXXVIII) Slide through courtesy of Dr Granville Bennet

systolic murmur over the apex rate 98 Blood pressure was 140/85 X ray showed heart normal in size and shape Liver was not palpable but spleen

was definitely enlarged 2 3 fingers breadth below the costal margin, smooth and not tender Tendon reflexes were normal

Laboratory Examination—Urine (July 5 194-) showed specific gravity 1 030 no albumin no sugar and 8 white blood cells in 10 high power fields Bence-Jones protein reaction was negative Blood showed hemoglobin 60 per cent (Sahli) red cell count 3 750 000 white cell count 8 500 with differential of 3 5 per cent lymphocytes 1 5 per cent monocytes the platelets appeared normal The reaction to a Hinton test was negative Blood sedimentation rate (Westergren method) was 5 mm in 1 hour Blood (August 17 194-) showed hemoglobin 58 per cent (Sahli) the red cell count 3 460 000 A month later the hemoglobin was 53 per cent (Sahli) and the red cell count 3 170 000 Blood chemistry values were total cholesterol 178 mgm per cent phosphorus 4 4 mgm per cent calcium 10 4 mgm per cent alkaline phosphatase 4 6 Bodansky units total protein 7 gm per cent

X-ray Examination of the chest showed both diaphragms smooth with clear angles The lungs were free from infiltration and the heart was normal in size and shape X ray examination of the femora lower legs lateral skull and knees revealed a most widespread and remarkable change of the bony structure in the left clavicle the upper ends of the left and right humerus the lower ends of both femora the upper and lower ends of both tibia and fibula These changes were present also in the pelvis and in the skull of the parietal bones The changes consisted of osteolytic and scleros ing cyst like lesions

Follow up Notes—While in the army this man underwent the normal basic training period Later he was hospitalized for headaches At this time most extensive bone lesions were rediscovered by x-ray The diagnosis of eosinophilic xanthomatous granuloma was established again by bone biopsy At present despite his most extensive bone lesions the patient works as a clerk He limps slightly but has no other complaints

Clinical Features

General Symptoms—The patients are mostly unaware of their bone lesions At the outset of the disorder they do not complain about bone pain The lesion may be accidentally found by x-ray examination Later a dull ache is experienced especially if the lesion is near the joint It is this painful stage the bone lesions usually are discovered

X-ray Findings—The lesion is mostly osteolytic in nature with well defined borders quite similar to fibrocystic bone lesions It should however be kept in mind that in rare cases the lesion may be diffuse giving a moth eaten appearance of the bone not unlike that in Gaucher's



Fig 79 Atypical osseous lesion of eosinophilic xanthomatous granuloma of the bone with sclerosing lesions in both tibiae in contrast to the usual osteolytic pseudo-cystic lesion verified by biopsy (Dr Sam Mueller Houston Texas)

disease There may be in rare cases hyperostatic features together with moth eaten appearance as shown in Fig 79 The location of the lesions is not characteristic of the disease and they may be found in any part of the osseous system as well as in the vertebrae The skull pelvis and the upper part of the femur are involved frequently

Differential Diagnosis

In the differential diagnosis all diseases where osteolytic bone lesions are a feature such as neurofibromatosis bone cysts plasmocytoma (myeloma) Gaucher s disease Hodgkins disease Ewing s tumors as well as metastatic bone lesions have to be considered If no other features of eosinophilic xanthomatous granuloma (Schuller Christian disease lipid granuloma) are present the diagnosis has to be verified by the histo-

was definitely enlarged -3 fingers breadth below the costal margin, smooth and not tender Tendon reflexes were normal

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necropsy suggested that the condition was probably of infectious etiology Griffith[32] (1924) and Weidman and Freeman[102] (1924) were the first to prove by their histological studies the xanthomatous nature of the xanthoma nodes involving the brain and membranous bones Rowland[91] (1928) who added two new cases of the Schuller Christian syndrome to the literature proved by extensive histological studies that this syndrome belongs to the group of xanthomatous diseases This relationship had not been recognized by previous authors

Chester[11] (1930) describing several cases of bone xanthomatosis added new histological material in order to separate the Schuller Christian syndrome from other xanthomatous diseases

Chester recognized the granulomatous nature of the lesions and distinguished this type of granuloma which he designated as lipoid granulomatosis from other diseases of a granulomatous nature Fraser[26] contributed an excellent histological and clinical study of the bone lesions and also adopted the name lipoid granulomatosis Thannhauser and Magendantz[96] demonstrated on the basis of numerous clinical and chemical studies that the Schuller Christian syndrome is the manifestation of a systemic disease which may occur as a monosymptomatic form (skin or bones) a trisymptomatic form (dura brain bone) (Schuller-Christian syndrome) or as a polysymptomatic systemic disease (skin dura brain lungs pleura pericardium osseous system lymph nodes liver and spleen) These authors showed that the accumulation of cholesterol and its esters in this systemic disorder is found only in the organs involved while the cholesterol content of the serum is normal They therefore concluded that the accumulation of cholesterol in the organs involved is not due to cholesterol infiltration from the blood stream but to a new formation of cholesterol in the same cells where it is built and accumulated Since the serum content of cholesterol is normal the clinical designation of essential xanthomatosis of the normocholesteremic type was used for these systemic manifestations

The histological studies of Farber and coworkers[1, 31] as well as those of Holm Teilum and Christensen[41] demonstrated that the histological lesions occurring monosymptomatically in the osseous system designated by Lichtenstein and Jaffee[59] as eosinophilic granuloma of the bone are histologically identical with the lesion found in the Schuller Christian syndrome In the former sections it has been stated repeatedly that the term eosinophilic granuloma' for the Schuller Christian syndrome leads to misunderstanding and therefore is unsatisfactory Since the accumulations of eosinophiles during the reticulohistiocytic prolifera

logical examination of a biopsy specimen and possibly its chemical analysis for cholesterol content

Treatment

The bone lesions of eosinophilic xanthomatous granuloma in contrast to the manifestations of visceral lesions respond fairly well to x ray treatment (Sosman[89]) They have a natural tendency to recede and disappear sometimes without treatment Diet therapy is as in other forms of this disease without effect

4 Schuller Christian Syndrome Osseous Lesions of Eosinophilic Xanthomatous Granuloma Defects in the Membranous Bones of the Skull, Exophthalmos and Diabetes Insipidus

Introduction

Hand[3,4] (1893) described a three year old child with an unknown kind of skin eruption Yellow nodes were observed in the skull with gaps in tabula externa and interna The autopsy revealed small yellow nodules in the liver and spleen, jaundice had not been present during the lifetime of the patient Hand did not recognize the disease and considered a differential diagnosis of tuberculosis or gumma both infectious diseases producing inflammatory granuloma His titles in 1893 were general tuberculosis' and polyuria and tuberculosis', in 19-1 he published a paper with the title Defects of membranous bones and polyuria in childhood is it dyspituitarism "

Kay[15] (1905) presented the case of a seven year old child with a similar triad of symptoms—bony defects of the skull exophthalmos and diabetes insipidus which he regarded as acquired hydrocephalus with atrophic bone changes Schuller[83] (1915) also reported the same clinical triad in a sixteen year old patient In this case the bony defects in the skull gradually became smaller almost disappearing in later years Christian[12] (1919) observed the same syndrome in a five year old girl who subsequently recovered apparently spontaneously Both Schuller and Christian regarded the affection as a manifestation of pituitary dys function

Thompson Keegan and Dunn[99] (19-4) who made the first complete

Christian syndrome are described in the section on Histology and Pathology in this section

Incidence

The Schuller Christian syndrome was considered a rare disease up to 1935 At that time sixty cases had been collected Numerous additional cases meanwhile have been described This syndrome is observed in white people It occurs mostly in children and infants cases in adults are rare Thannhauser and Magendantz[90] described a fifty one year old man (Case XL) with this disorder In the following pages two more adult cases (Case XLI and XLII) are reported The disease affects males more than females No familial occurrence of eosinophilic xanthomatous granuloma (Schuller Christian syndrome) has been observed There is an observation of identical twins only one but suffered from xanthomatosis of the bones

Clinical Cases

Case XLI —C S a fifty one year old Italian carpenter noticed multiple excrescences in the region of his right ear and at the external canthus of his right eye when he was thirty five years old (Figs 80 and 81) There was sero hemorrhagic discharge from the right and several years later from the left ear as well When the patient was forty one numerous soft tender masses appeared on his head and drained sero hemorrhagic fluid Some of the older lesions ceased draining subsequently but other new ones appeared and drained At about that time bilateral exophthalmos appeared He also began to suffer from polydipsia and polyuria He was told at a hospital that his skull was paper thin and that he had but three or four months more to live He continued working however until at forty seven he fell down the stairs and fractured his left femur and right humerus In the Beth Israel Hospital Boston a plaster cast was applied He was treated with irradiation by roentgen rays His fractures healed the draining of the sinuses of his skull ceased He was up and about feeling well His diabetes insipidus responded to a preparation of pitressin in oil Fasting blood sugars frequently were elevated and a glucose tolerance test showed a diabetic type of curve At no time was sugar present in his urine His blood cholesterol values varied from 145 mgm per cent to 235 mgm per cent during his hospital stay

tion is only one of the stages in the various phases of the lesion its designation as "eosinophilic granuloma" is misleading because "eosinophilic granuloma" is not a disease entity but only a phase of the development of the lesion Accumulation of eosinopiles may occur also without xanthoma formation in entirely different diseases as Hodgkin's granuloma[13], eosinophilic granuloma of the skin[34], and Loffler's syndrome[6]

The formation of xanthoma cell (xanthomatous phase of the lesions) is as characteristic for Schuller-Christian syndrome as the accumulation of eosinophiles in the early phase of the lesion If one does not prefer to use the older names of Schuller-Christian syndrome or 'lipoid granulomatosis', the designation eosinophilic xanthomatous granuloma" of the monosymptomatic as well as the polysymptomatic forms of the systemic disorder seems more appropriate, even if its name does not embrace the reticulo-histiocytic proliferation of the lesion

Morbid Anatomy

The defects of the membranous bones of the skull (Fig 82) vary in size and are asymmetrical in shape and distribution The inner and outer tables usually are involved In advanced stages of the disease almost the entire vertex and the base of the skull may show defects The xanthomatous nodes in the dura are yellow, rubbery masses, sometimes assuming tumor-like proportions They arise in the inner and outer surfaces of the dura and periosteum overlying the calvarium If they originate on the base of the brain, they not only displace the pituitary but may also extend forward into the orbit nasal sinuses and mastoid regions The pressure of these masses also may dislocate the bulbus of the eye and cause exophthalmos of unusually disfiguring appearance

The older lesions which show only a few scattered foam cells consist mainly of a firm brownish fibromatous scar tissue The vertex of the skull especially may contain tumor-like swellings or cyst like formations filled with a reddish-brownish, semi fluid detritus Small xanthoma may develop in both jaws and especially in the sockets of the teeth which become loose Histological examination reveals lesions characteristic of eosinophilic xanthomatous granuloma in the bone marrow of the jaw and in the tips of the roots of the teeth[93, 30a, 30b, 8b] Small yellowish-white spots are scattered through the bone marrow of the long bones

The histology of the skin and the osseous lesions in the Schuller

member in his family with a similar condition or other manifestation of xanthomatosis

The patient was admitted to the Diagnostic Hospital of the New England Medical Center in January 1937. He was slightly obese and not icteric. He was also very thirsty and urinated at frequent intervals. His skull was strikingly deformed showing a number of bulging areas and depressions which involved also the facial part of the head. The depressions were hole like and funnel shaped, the surrounding bone was not thin, flexible or tender. None of these areas showed secretion. There was marked exophthalmos of both eyes (Fig. 81). In the skin of both upper and lower lids there were several soft swellings lighter and flatter than xanthelasma (Figs. 80 and 81). His pupils were round, reacting to light and accommodation; his fundi showed no abnormalities. Both ear canals were filled with soft, yellowish material which revealed no cholesterol crystals on microscopic examination. There was total nerve deafness. The mucous membranes of the mouth and throat showed no abnormalities. Heart and lungs were essentially normal. Blood pressure 160/98. In the lower abdomen the distended bladder extended above the umbilicus. After removal of 1 000 c c of urine the bladder was still palpable. The right humerus and left femur were markedly deformed and shortened with limited motion in the right elbow and left knee joint. The skin of both hands was dry and hyperkeratotic. This condition was more marked over both lower legs where there were large grayish brown scales and onychogryphosis of the nails of both big toes. The thoracic spine was kyphotic and the patient's gait awkward, stiff and limping. He could walk only with the aid of a cane. No definite abnormalities of the central nervous system were demonstrated except the bilateral deafness, an occasional coarse tremor of the head and the ischuria paradoxa.

The volume of the urine varied from 4 000 to 9 600 c c daily. It contained from 35 to 75 grams of sugar daily. On a diet of carbohydrate 150 grams, protein 80 grams and fat 100 grams with 0 units of insulin twice daily he remained sugar free. Under insulin treatment the urine volume diminished to between 1 00 and 500 c c daily.

Fasting blood sugar varied from 4 to mgm per cent. The glucose tolerance curve was diabetic in type.

	Serum calcium	10 mgm %
	Serum phosphorus	4 3
	Icteric index	10
	Phosphatase 75 units in 100 c c serum	
1/11/37	Serum total cholesterol	19 mgm %
	Serum free cholesterol	67
	Serum cholesterol esters	1



Fig 80 Exophthalmos deformity of the skull and orbits Note that the eyes are not in parallel line because of the protruding masses on the right side (case XI)



Fig 81 Xanthoma protruding from both orbits (case XI)

During the following years he developed a gradual unrecognized disten tion of the urinary bladder He also became totally deaf He knew of no



Fig 83 Roentgen ray of the humerus showing spontaneous fracture and xanthomatous pseudo cysts (case XL)

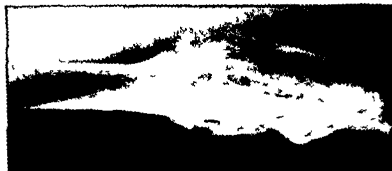


Fig 85 Roentgen ray of the femur showing spontaneous fracture and xanthomatous pseudo cysts (case XL)

Case XLI Adult Case with Diabetes Insipidus, Epileptic Form, Seizures and Bone Lesions

Mrs E W D a 49 year old secretary was referred to the author by Dr William H Mason of Fall River The patient reported that the diagnosis of diabetes insipidus was made when the patient was 37 years old At that time there was a large fluid intake and output There was also loss of appetite The patient described her condition as follows I was unable to go by a water fountain without drinking I was always thirsty and would get up every half to one hour to drink and void My mouth felt spongy I recall that my menstrual flow would be more watery than blood Keeping an ice cube in her mouth would not satisfy the thirst I would prefer a long drink to food In June 1935 pituitrin was started with the patient

/3/37	Serum total cholesterol	00 mgm %
	Serum free cholesterol	56
	Serum cholesterol esters	144

Basal metabolic rate minus 1 per cent



Fig. 82 Roentgen ray of the skull Geographical skull (case XL)

The cholesterol figures showed normal total cholesterol and normal cholesterol esters in conformity with the figures reported in similar cases in the literature

Roentgen rays of the skull (Fig. 82) showed what has been described as a skull resembling a geographical map the tables of the skull being irregularly eroded in areas varying from pin point size to large irregularly shaped defects The sella turcica was not particularly enlarged There was extreme increase in density at the base of the skull involving both mastoids sphenoids and roofs of the orbits Roentgen-rays of the humerus (Fig 83) showed osteolytic lesions as did the femur (Fig 84) as well as healing spontaneous fractures with callous formation There was a definite erosive lesion at the outer circumference of the right ilium just above the head of the femur

Biopsy Tissues of yellow hue of excised nodules of the dura contained more granulomatous tissue than is found in tuberous xanthoma of the skin Histological sections (Figs 88 and 89) showed scattered xanthoma cells and conglomerate nests of eosinophilic cells in the granulomatous tissue Giant cells and exudate cells were also observed in the granulomatous nodules There was no outstanding difference in the histological findings of the xanthomatous nodule of the dura and other xanthomatous tissue

would fall off She still has scars and sores from last summer Two weeks ago intranasal pituitrin rather than the injections were recommended

Three years ago the patient was aware of a sensitive area over the left parietal region At this time her ears felt stuffed One year ago she noticed

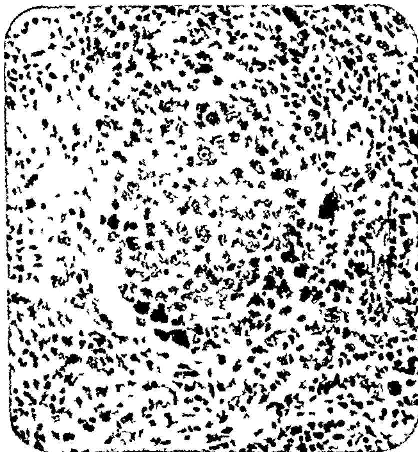


Fig 87 Xanthomatous nodule of the dura Note large amounts of granulomatous tissue and nests of eosinophiles (case XL) Histologic al slide through the courtesy of Dr M J Schlesinger

a large lump on the left side of her neck X ray of the skull was taken because of a tender area on her head which later felt indented they revealed a hole in the skull The patient returned to her physician Hospitalization was advised and x rays were taken of the long bones and skull The diag

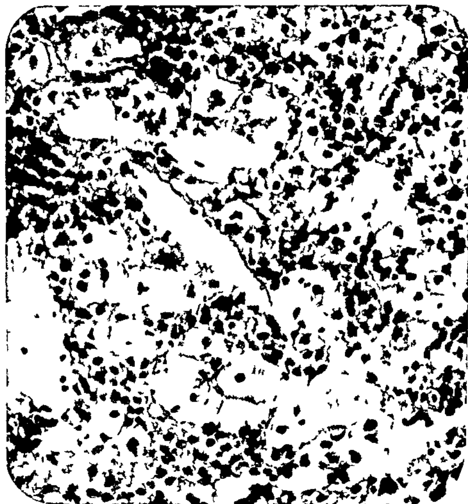


Fig. 85. Xanthomatous cells of a xanthomatous nodule of the dura. Note large amounts of granulomatous tissue (case XI). Histological slide through the courtesy of Dr. M. J. Schlesinger.

receiving one injection of one c.c. of pituitary every night. Obstetrical pituitrin was good for six hours and the "surgical" for eight. It seemed to quench her thirst more than her desire to void. After taking an injection she would go to the bathroom once during the night. After twelve hours the pituitrin effects would have worn off and her desire for fluid would return. The patient continued with the injections until March 15, 1947. Approximately one year ago the patient first developed sores at the site of the injections. Resembling little ulcers they would dry up and the crust

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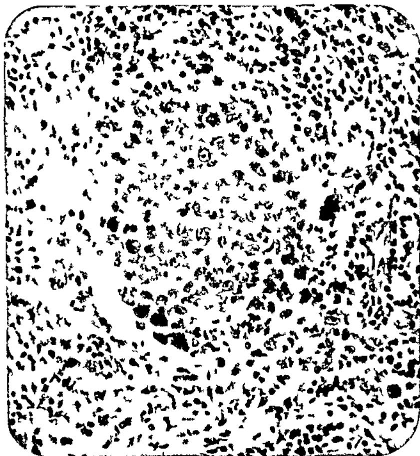


Fig 86 Xanthomatous nodule of the dura Note large amounts of granulomatous tissue and nests of eosinophiles (case XL) Histological slide through the courtesy of Dr M J Schlesinger

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nosis of Schuller-Christian syndrome was made. Twelve years ago the patient had suffered from pains in the back of her head. At that time skull x-rays were negative. The patient has had blurring vision occasionally. Sometimes she experiences the sensation of pressure on her eyeballs. There has never been any exophthalmos to her knowledge. She has headaches regularly and feels as if her head swells up. The eyes get blurry, and the skull defect in the left parietal areas becomes sensitive. Her hearing is not as acute as formerly. If she pulls down on her ear lobes her hearing seems to improve. At times there is a pussy discharge from both ears. The swelling on the left side of her neck, which seems to vary in size, is non-tender. Some days it is harder than others. This is the only lump of which the patient is aware. There have never been any skin changes to her knowledge. Two weeks ago she had an attack of syncope. There was no aura. She was seized by this attack while voiding and states that she did not know she had passed out. Her husband said that one arm was jerking and that she frothed at the mouth. As a result of her fall she received a black eye. She believes that she was unconscious for approximately three hours. When consciousness was regained she had a funny feeling in the stomach and the calves of both legs pained terribly. She recalls another attack of syncope in September, 1946, when she was unconscious for one-half hour.

Her mother died two weeks ago of a shock at the age of 77. The father is living and well at the age of 80. There are three brothers and two sisters all living and well. No family history of cancer, tuberculosis, kidney disease, heart disease, diabetes, nervous disease or convulsions.

Physical Examination.—On admission pulse was 76, temperature 98.I, respiration [illegible]. The patient is 5' 4" tall and weighs 139 pounds. Blood pressure, right arm, recumbent position, is 130/80. The patient, a moderately obese woman in no acute physical distress, is pleasant and cooperative and seems to enjoy the discussion of her present illness. Her skin is dry and warm. The lower portion of the abdomen and the lateral aspect of both thighs show numerous ulcerated scarred areas. The skin in these regions is indurated. There is no icterus, no petechiae, no cyanosis, no anemia, no clubbing of the fingers. The face is symmetrical. There is no sinus or mastoid tenderness. In the left parietal region there is an area about the size of a five cent piece which is devoid of bone. Considerable tenderness is elicited on light pressure in this region. There are areas of tenderness about the skull. No bruit was heard in this region. There are no exostoses. Auditory acuity is good. Weber test lateralizes to the left. Tympanic membranes are intact. Pupils are small, round, equal and react briskly to light and accommodation. Extraocular movements are in full range. There is no nystagmus, blepharitis or conjunctivitis and no exophthalmos. There is some slight lidlag. Ophthalmoscopic examination reveals well defined discs with no retinal lesions, hemorrhages or exudate. Nose shows no septal de-

flection rhinitis performation or polyps Teeth are in good repair no cheilosis is present Tongue projects in midline papillae are prominent There is no stomatitis gingivitis glossitis pharyngitis or areas of pigmentation or xanthelasma An elongated mass is felt which seems to extend from the left postauricular region almost to the left supraclavicular fossa (enlarged lymph nodes) There is an enlarged node in the right paratracheal region There is no axillary adenopathy Lungs are clear to auscultation and percussion there are no rales Diaphragmatic excursions are good Heart is normal in size and position rate normal rhythm regular no murmurs sounds of good quality The abdomen is flat symmetrical tympanitic with no shifting dullness no fluid wave Liver edge is just palpable Spleen could not be palpated Kidneys could not be felt No abdominal masses felt The scars and the induration of the skin on the lower abdominal regions have been mentioned Extremities are symmetrical with no varicosities no peripheral edema Dorsalis pedis pulsations are good Muscular system shows no atrophy paralysis fibrillation or tremor Muscle tone and strength are good Coordination tests are well performed Sensations are intact Reflexes are equal and active bilaterally No pathological reflexes were elicited Pelvic examination shows the external genitalia normal perineal tone good marital introitus cervix is normal in position is nulliparous and freely movable Uterus and adnexa were not felt Rectal examination shows external tabs The stool was brown

Laboratory Findings—Urine specific gravity 1 001 1 003 sodium content 0 0 , gm per cent chloride 0 046 gm per cent Serum chlorides are 99 mill equival serum sodium 137 mill equival Hemoglobin is 61 per cent 9 6 gm red blood cells 4 560 000 color index 0 66 white blood cells 1 600 basophiles platelets normal Blood sedimentation rate 90 in 1 hour Serology for syphilis negative Lumbar puncture shows protein 8 mg per cent no cells Lipid analysis of the clear serum is shown in Table XXVIII

TABLE XXVIII

Total fatty acids	510 mgm per cent	
Neutral fat	175	
Total phospholipids	328	
Total cholesterol	34	
Free cholesterol	6	
Cholesterol present as esters	174	(74% of total)

X ray Examination—Skull shows a large irregular circular defect in the left posterior parietal bone The pelvis and upper right femur and the left anterior second rib show similar defects The most marked involvement

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thoma was made but he was returned to duty with no recommendations for treatment He got along perfectly well with no symptoms until February 1944 when he was ordered into the hospital for examination The skin lesions on his eyelids now were somewhat larger and the small reddish brown spots over his arms and body were marked These eruptions varied in size from one to two millimeters in diameter they were not painful and did not itch There were no systemic symptoms at this time When he was sent to the Woodrow Wilson Hospital in Staunton Virginia in February 1944 he was examined by a dermatologist who diagnosed his condition as xanthomatosis with petechiae The doctor told him that there was nothing that could be done for his condition and advised him to go back to duty and forget about it At this time the lesions over his eyes were a chamois yellow color slightly raised and painless and did not itch Similar lesions were visible on his scalp

His outfit went overseas and he had no more trouble until June 6 1944 In his office one morning at the quartermasters headquarters in London England he suddenly turned to a friend saying he felt sick He was nauseated and slightly dizzy He arose and went to the bathroom thinking that he might vomit and upon entering fell to the floor unconscious Later some friends told him that he had a convulsive seizure He remembers no premonitory symptoms and was unconscious for 14 hours During this time he did not bite his tongue or soil his clothes He was sent to the 6 nd General Hospital and had no additional seizures During his hospitalization the diagnosis of meningococcemia was made because of the presence of the petechiae and the convulsive seizures He was given sulfonamides which he took for several days although he states that there was no evidence of chills or fever On the 4th of July 1944 he returned to duty The xanthomata of the eyelids as well as the numerous petechiae over the arms and body now were quite pronounced

No unusual symptoms occurred until February 1945 While he was in Belgium he began to have spells of dizziness which would occur frequently during the day for two or three days and then subside He describes this as a sense of giddiness and unsteadiness on his feet There was no actual vertigo He was hospitalized again and the dizzy spells finally stopped altogether He returned to duty without incident until May 3 1945 when he was in Ludwigshaven Germany He arose one morning feeling slightly dizzy ate breakfast and walked to his office As he started up the steps to the third floor of the building he felt weak and dizzy and decided to go to the dispensary instead Somewhere on the way he had a slight convulsive seizure and was sent to the hospital for fifteen days All during his hospitalization he felt extremely dizzy and one day had a convulsive seizure of a minor nature while he was in bed

After being sent back to duty he felt well until August 15 1945 Sitting

is in the upper right femur and in both iliac bones There is some reactive new bone *formation about the defect in the ilia* The *outstanding feature* however is the defects along the lateral aspect of the right acetabulum which shows that these lesions are not cystic but rather destructive The right 5th posterior rib shows a large defect with somewhat different type apparently the site of the biopsy The lungs do not show infiltration The right and left lower and upper extremities show no bony involvement

Examination of lower portions of both femora shows evidence of involvement of the right femur to the middle third The left femur shows involvement of the middle third with expansion of the shaft The lateral film of the chest shows no involvement of the dorsal vertebral bodies

A small defect is seen in the left anterior rib measuring approximately 8 millimeters in diameter A portion of the right 5th posterior rib is missing near the axillary line over a distance of approximately 1½ cm apparently the site of a biopsy The lung fields are clear The heart is not enlarged

Electroencephalogram is normal

Consultation Note—Dr Ray Adams (Neurologist) Patient undoubtedly has a dural lesion overlying the left parietal lobe resulting in right side *convulsive seizures In addition there is a long history of diabetes insipidus* There is undoubtedly some involvement of the base of the skull in this process with involvement of the subthalamic region There seems no indication for any operative intervention The patient's convulsive state can best be controlled by anti convulsive medication

Summary—This patient has extensive bone lesions of eosinophilic xanthomatous granuloma In addition to the skull long bones and pelvis all the ribs are involved The lymph nodes especially on the left side of the neck are enlarged The patient has dural lesions overlying the left parietal lobe The right-sided convulsive seizures are due to xanthomatous lesions The diabetes insipidus hints to an involvement of the brain in the hypothalamic region

Case XVII Skin Lesions of the Petechial and Plain Type Bone Lesions Diencephalic Autonomic Seizures and Attacks of Petit Grand Mal (Epilepsy)

A 38 year old white male R C C from Lexington Kentucky was referred by Dr Thornton Scott of that city in December 1946 (Fig 87) The patient dates his present illness from July of 1943 He was in the army at Camp Lee Virginia when he first noticed small reddish brown spots over his arms and body At about the same time he observed also yellowish brownish discoloration over the upper and lower eyelids as well as around the hair line of the scalp At the hospital a diagnosis of xan

in a staff meeting in Frankfort, Germany he suddenly slumped unconscious fell to the floor and had a convulsive seizure He was told later that he had two more convulsions on the way to the hospital These were described as typical with clonic movements tonic movements and tongue biting He was unconscious for a total period of 12 to 14 hours The diagnosis was a probable brain tumor On the basis of his past history of suspected meningococcemia he was started on penicillin which he took every three hours for several days On September [illegible] 1945, he was evacuated to McGuire General Hospital in Richmond Virginia The patient was now feeling quite well with no particular symptoms The small reddish brown petechiae on the skin were occurring sporadically in showers The yellow areas around his eyes and on his scalp were progressing very slowly if at all He believed however that his scalp was now involved more extensively than it had been during the previous year

In October 1945 the patient had another convulsion He was unconscious for several hours and bit his tongue but suffered no sphincter loss On November 23 1945 he had a severe attack of dizziness for which he was put to bed but he suffered no real convulsion He was given dilantin sodium 3 capsules daily with phenobarbital grain 1 three times daily Finally on January 16 1946 he was retired from the Army with the diagnosis of epilepsy and xanthomatosis

After his return home he had an attack of dizziness and amnesia on February 10 1946 He awakened one morning and asked his wife where he was She replied that they were in Lexington Kentucky but he did not remember his being there He recognized his wife later and remembered past events clearly but had no awareness of his present situation The dizziness and amnesia lasted for about four hours before his memory returned He again felt well until July 24 1946 when he awakened one morning and noticed small red spots covered his right arm He felt dizzier than usual as well as generally weak and fatigued The red spots and the dizziness lasted for several days before they subsided On August 13 1946 he had an episode when he could not think clearly for 48 hours He remained in bed and felt confused amnesic and dizzy During this period the patient was not working except for doing minor repairs and cleaning up around a small home he had purchased On October 17 1946 he awakened one morning with his left forearm throbbing with pain so severely that it caused him to cry He applied liniment heat and massage with no alleviation However aspirin taken every three hours finally gave some relief Since that time the patient has continued to have transient dizziness weakness fatigue loss of pep and energy as well as the petechiae and skin lesions on his head and face

During the past year intermittent hot flushes have been occurring 6 to 8 times weekly lasting [illegible]0 minutes The patient describes these as just a feeling of flushing with weakness dizziness and sweating During one of

his numerous examinations he had been told that he had an irritable carotid sinus He has to avoid looking up because of extreme dizziness His scalp recently has seemed to tingle all the time and he dislikes wearing hats because of the increased sensitivity of his scalp During the past two years he has developed a sensitivity to odors such as perfumes and frying foods These smells make him quite nauseated and dizzy forcing him to go out immediately for fresh air Being in a crowd makes him uncomfortable as well as nervous panicky and tremulous He thinks that there has been a definite diminution of memory during the past year He will go somewhere with his wife but will not remember it later He has not the slightest recollection of a two week inspection trip he made to Florida in 1944 Upon rereading his notes he does not remember even the slightest incident that occurred His memory for long past events seems normal The patient seems to have developed a slight deafness within the past year

There have been no serious illnesses or operations The patient denies even the usual childhood diseases

Mother and father are living and well aged 69 and 65 respectively He has three brothers and one sister all living and well There is no family history of diabetes cancer tuberculosis heart trouble arthritis nervous disease epilepsy xanthomatosis

Physical Examination—Height 6 weight 166¼ temperature 98 6 F pulse 90 respiration 0 blood pressure right arm 120/70 left arm 1 0/80 The patient is a well developed and well nourished white male 38 years old intelligent alert and cooperative and in no acute distress at the present time The head is symmetrical Overlying the scalp (Fig 87) in an area extending completely over the scalp is a raised brownish yellow confluent lesion which is dry non scaling and appears to be merely a thickening from infiltration of the skin Similar lesions occupy areas over both upper eyelids The lower lids show smaller areas of a chamois tan color *slightly* raised non tender and appearing roughly like fine-grained orange skin (Fig 87) Eyes the pupils are round and equal react to light and accommodation the sclerae are clear the extraocular movements are normal Ears the canals are open the membranes are smooth and glistening there is a slight amount of cerumen there is possibly a slightly diminished hearing on the right side with no evidence of hearing defects on the left by a gross test Nose the mucous membrane is pink and dry the septum is in the midline there is no obstruction to the air passages Mouth there are two upper molars that have been removed from each side the tongue *protrudes in the midline* and shows no atrophy of the papillae the buccal and pharyngeal mucosae are normal and show no areas of pigmentation Neck there are a few palpable lymph nodes in the anterior cervical chain the isthmus of the thyroid is palpable but the gland itself is not enlarged there is no rigidity of the neck limitation of motion or tenderness



Fig 8, Xanthelasma of both eyelids and xanthoma plana of the scalp chamois in color (case XLII)

X ray Examination—Both humeri reveal nothing abnormal There are areas of medullary thickening in the lower portion of the shaft of each radius as well as similar irregular coalescent areas of increased density in the lower portion of the shaft of each femur and the upper portion of each tibia Some



FIG 88 Petechiae like lesions over the back (case XLII)

of the films show the portion of the cortex which was removed for biopsy These areas do not look like regions of demineralization but rather regions where there is increased thickening of the medullary bone (hyperostosis) It is not the usual osteolytic appearance which is seen in other cases of this type

The bones of the calvarium show irregular texture and appear slightly thickened There are numerous small areas of diminished density which represent venous lakes *There is no definite evidence of any* punched out areas such as one might expect to see in Schuller Christian syndrome The pineal is calcified but not displaced from the midline The pituitary fossa

The chest is symmetrical, the expansion is equal with normal excursions, the vocal fremitus is normal front and back the percussion is resonant throughout the breath sounds are vesicular, there are no rales or friction rubs whispered and spoken voice sounds are normal Heart there are no unusual pulsations over the precordium, the borders of the heart are percussed within normal limits the heart rate is 90 the rhythm is regular the sounds are of good intensity and quality, there are no murmurs of any description On further examination of the carotid sinus pressure over either left or right carotid body produces marked slowing of the heart with subjective symptoms of dizziness and faintness but during this examination no seizures or fainting occurred

The abdomen is symmetrical soft and non tender Neither the liver nor the spleen is palpable The liver dullness is percussed in the 6th interspace splenic dullness is within normal limits There are no scars masses or herniae There is no evidence of intraabdominal fluid Percussion over either kidney elicits no tenderness *Over the skin of the shoulder arms, trunk and legs there are numerous scattered reddish brown petechiae like spots varying in size from pin heads to 2 millimeters in diameter These are pleomorphic in size and appearance but are not raised above the skin They are not tender* (see Fig 88) Normal male genitalia both testes are in the scrotum there is no enlargement or tenderness of them there are no lesions or discharge from the penis Rectal examination reveals good rectal sphincter tone there are no hemorrhoids the prostate is normal in size and consistency and is not unusually tender The skin of the extremities is as already described There is no pain tenderness or limitation of motion in any of the joints There is no edema of the lower extremities clubbing of the fingers or tremor of the hands There is a slight amount of epidermophytosis

The patient's sensorium is clear There is no amnesia or confusion at the present time He does complain of being slightly dizzy The cranial nerves are intact The deep and superficial reflexes are present and normal Vibratory sense is normal Romberg's sign is negative

Laboratory Findings Urine shows specific gravity 1 011-1 0 1 no sugar no albumin Hemoglobin is 64 per cent 13 1 gm red blood cells 4 200 000 color index 1 white blood cells 9300 polynuclear cells 64 % lymphocytes 25% monocytes 11 eosinophiles 0 platelet 3 4 000 Blood sedimentation rate 25 in one hour Serology is negative Serum is transparent Neutral fat is normal Total cholesterol is 196 mgm per cent free cholesterol 48 mgm per cent cholesterol present as esters 148 mgm per cent (75 per cent of total cholesterol) Total serum protein is 5 5 gm per cent albumin 3 8 gm per cent globulin 1 7 gm per cent calcium 10 1 mgm per cent phosphorus 38 mgm per cent Alk phosphatase is 3 6 units Lumbar puncture showed protein 80 mgm per cent 2 lymphocytes Its pressure was 180-450 mm with delayed rise

The saw toothed affair strongly suggests an atypical seizure allied to psychomotor spells

Approximately three minutes after overbreathing a peculiar focal slow wave discharge appeared in the left hemisphere centering around the left temporal area Within thirty seconds the patient had a confused period in which he could not understand spoken commands developed a rapid pulse and appeared to be gliding toward a spell He cleared in about a minute The patient's wife who was permitted to observe him at this time claimed that this is how he looks when he goes into a spell

The electroencephalogram gives evidence of diffuse cerebral disorder which has an epileptic component The most striking finding suggests atypical seizures allied to psychomotor epilepsy The possibility of a focus within the left hemisphere should be borne in mind

Summary —The patient has many petechiae like lesions characteristic of eosinophilic xanthomatous granuloma in addition to his permanent plain skin xanthoma The latter involved a large area of his scalp as well as his eyelids He had attacks of epileptic seizures of the grand mal type as well as of the diencephalic autonomic type significant of the involvement of dura and brain in the xanthomatous and granulomatous process The lymph nodes of the cervical chain were also involved X ray of the femora showed not the typical osteolytic cyst like lesions but areas of greater density (hyperostosis) in the lower part of the femur Biopsy of the femur proved that the bone changes were due also to eosinophilic xanthomatous granuloma with the prevailing of its fibrotic phase Diabetes insipidus was never present at any time

Clinical Features

The triad of symptoms consists of bone defects in the membranous bones exophthalmos and diabetes insipidus Children (Fig 90) are affected most frequently but may recover Sometimes the disease is prolonged extending through youth and in rare instances the syndrome is found in adults (see Cases XL XLI and XLII)

The onset of the disease is insidious The child usually is brought to the physician because of excessive thirst exophthalmos and defective skull formation Manifestations like sore mouth or teeth which fall out may bring the disease into the open when the child is between two and four years old Xanthoma disseminata and petechiae like lesions appear Sometimes the skin lesions may be present already from the beginning of the disease The children usually become anemic Their growth is retarded but they become fat In some cases death results from inter

is normal in size and configuration There is no erosion of the clinoids or of dorsum sella

Biopsy of skin, petechiae like lesion (see Fig 89)

Electroencephalogram—This is a definitely abnormal tracing with a great deal of irregular activity at all times in the 5 8 per second range of fre



Fig 89 Skin (case XLII) This field was selected to show an acute inflammatory reaction involving a capillary in the reticular layer of the corium Just to the left of the center the capillary is moderately dilated and is cut in cross section The same capillary just to the right of center is cut longitudinally It is apparent that the capillary is the central point in the inflammatory reaction The lumen is obscured by fibrin which fills the lumen in one area and saturates the wall and surrounding tissue

The most striking feature of the entire reaction is the infiltration with large swollen acidophilic endothelial leucocytes There is inflammatory edema and there is fresh bleeding into the surrounding tissue Polymorphonuclear leucocytes are found singly and in small clusters of three and four In general the dominating cell is the endothelial leucocyte *Diagnosis* Hemorrhagic and histiocytic capillaritis' (H I MacMahon)

quency Slower activity appears from the left side over a wide area than from the right On occasions abortive single spike and wave discharge appears in the left hemisphere

During overbreathing a number of saw toothed discharges with positive spikes appear This activity again is most marked in the left hemisphere

The saw toothed affair strongly suggests an atypical seizure allied to psychomotor spells

Approximately three minutes after overbreathing a peculiar focal slow wave discharge appeared in the left hemisphere centering around the left temporal area Within thirty seconds the patient had a confused period in which he could not understand spoken commands developed a rapid pulse and appeared to be gliding toward a spell He cleared in about a minute The patient's wife who was permitted to observe him at this time claimed that this is how he looks when he goes into a spell

The electroencephalogram gives evidence of diffuse cerebral disorder which has an epileptic component The most striking finding suggests atypical seizures allied to psychomotor epilepsy The possibility of a focus within the left hemisphere should be borne in mind

Summary —The patient has many petechiae like lesions characteristic of eosinophilic xanthomatous granuloma in addition to his permanent plain skin xanthoma The latter involved a large area of his scalp as well as his eyelids He had attacks of epileptic seizures of the grand mal type as well as of the diencephalic autonomic type significant of the involvement of dura and brain in the xanthomatous and granulomatous process The lymph nodes of the cervical chain were also involved X ray of the femora showed not the typical osteolytic cyst like lesions but areas of greater density (hyperostosis) in the lower part of the femur Biopsy of the femur proved that the bone changes were due also to eosinophilic xanthomatous granuloma with the prevailing of its fibrotic phase Diabetes insipidus was never present at any time

Clinical Features

The triad of symptoms consists of bone defects in the membranous bones exophthalmos and diabetes insipidus Children (Fig 90) are affected most frequently but may recover Sometimes the disease is prolonged extending through youth and in rare instances the syndrome is found in adults (see Cases XL XLI and XLII)

The onset of the disease is insidious The child usually is brought to the physician because of excessive thirst exophthalmos and defective skull formation Manifestations like sore mouth or teeth which fall out may bring the disease into the open when the child is between two and four years old Xanthoma disseminata and petechiae like lesions appear Sometimes the skin lesions may be present already from the beginning of the disease The children usually become anemic Their growth is retarded but they become fat In some cases death results from inter



Fig 90 Schuller Christian's Disease An Italian boy aged 3½ years showing extreme degree of exophthalmos He had diabetes insipidus extensive membranous defects and dwarfism His mentality was normal

current infection, in others the bone defects in the skull slowly disappear, and the children develop but always with some retardation

Fever—Fever of short duration but recurring in longer intervals is observed sometimes The etiology of the fever may be manifold It may result from softening and inflammation of either one of the nodes in the dura or of a xanthomatous node in the bone It may in fact even simu

late rheumatic involvement of one of the extremities because muscle and joint pain may occur simultaneously with the fever. The bone involvement in the extremities is revealed only by x-ray examination. Sometimes the fever may be the result of intercurrent cystitis because some of the patients have ischuria paradoxa. Fever may be caused also by involvement of the lung in the xanthomatous and fibrotic changes which may simulate bronchial pneumonia.

Skin.—Xanthoma disseminatum is not always present in the Schuller-Christian syndrome.

The characteristic location and color of the disseminated xanthoma have been described in an earlier part of this section. The petechiae-like lesions usually are observed in cases of acute development in early childhood but may occur also in adults (see Case XLII) together with xanthoma disseminata. Both types of disseminated skin lesions are important for diagnostic reasons. Their presence immediately suggests the diagnosis of xanthomatosis of the normocholesteremic type, i.e. eosinophilic xanthomatous granuloma. If such lesions are present one should search for lesions in bones, lungs and other organs involved in this systemic disease.

Exophthalmos.—The exophthalmos produces a disfiguration of both eyes (Fig. 90). A distorted, grotesque appearance results from the fact that both eyes are not in a straight horizontal line, one being usually higher or lower than the other. Sometimes the protusio bulbi is so marked that the cornea becomes injured and ulceration and panophthalmia result. No abnormality of the retina has been reported. Heath[3] has called attention to the changes in the internal structure of the eye.

The exophthalmos is due either to granuloma-like masses in the orbit or to destructive processes of the bony structure of the orbital region. It has been suggested that the exophthalmos in hyperthyroidism is caused by an improper balance of the autonomic nervous system. This assumption is not true in the case of the frog-like exophthalmos of the Schuller-Christian syndrome. Here it definitely results from a mechanical displacement by granulomatous tissue in the orbital region. Some believe it can be caused by intracranial pressure against which the bony orbit no longer protects.

Bone Changes.—Deformity of the skull may call attention to the bone defects of the skull. The patient sometimes may have vague pains in the skull. The bone defects are discovered by palpation of the deformed areas. A cyst-like swelling or tumorous excrescence occasionally may be felt. Pulsation of the brain may be observed also in these



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areas In addition there is sometimes a brownish serous fluid draining from the lesion

The bulging and swelling is found mostly on the scalp sometimes on the forehead X-ray examination of the skull reveals areas of bone rarefaction in the calvarium (Fig 82) and also at the base of the skull The bone destruction sometimes may involve not only the sella turcica but also the adjacent temporal and frontal regions Both tables may be affected Because the x ray film of the sharply defined defects has the appearance of a geographical map these skulls are accordingly designated as "geographical map skull"

In the Schuller-Christian syndrome osteolytic lesions are found in other areas of the skeleton in addition to the bony defects of the skull They are observed in the superior and inferior maxillae scapulae ribs vertebrae pelvis and long bones (Fig 83) Usually there is no pain If the patient has no bone deformity or limp the bone defects are only detected by x-ray examination

The x-ray shows that the defects with their sharply defined borders and round or oval shape in the long bones and pelvis resemble mostly bone cysts in appearance (Fig 83) The edges sometimes may be blurred because both bone destruction and bone repair may occur simultaneously in the lesions Large defects may even be filled in by new bone formation The spontaneous fractures, which occasionally occur in these lesions (Fig 84), may lead to the detection of the disease If the vertebrae are involved, there may be a compression fracture of the vertebral body with consecutive symptoms of medullary affection There is occasionally a thinning with some distention of the cortex of the long bone This is however only a localized distention involving only a small area The appearance is different from the diffuse thinning of the entire cortex which occurs in Gaucher's disease

Localized destruction of the maxillary bones causes the teeth to loosen and fall out Rowland described cases in which the roots of some teeth were eroded and looked as if they were sawed off Other authors reported a small granulomatous node on top of the root Spongy gums caused by a secondary inflammation may be an early indication of xanthomatous involvement of the roots of the teeth

If the lesions in the bones are located near the joints they may penetrate into the joints and involve them in the disease However an involvement of the distal joints should not be confused with the isolated perforation of a single granulomatous lesion into the joint

Mastoid and Sinuses—Some cases have been reported in which there

is a viscid brownish red discharge from the middle ear Xanthomatous affection of the mastoid bone may be first revealed by a mastoid operation The granulomatous masses may infiltrate into the sinuses also and produce local symptoms

Diabetes Insipidus—Polydipsia and polyuria are regular features of the Schuller Christian syndrome It has been pointed out already in the section describing the isolated occurrence of diabetes insipidus and xanthoma disseminatum without bone changes that in such cases the specific gravity of the urine is higher than 1 003 and mostly around 1 010 These higher figures do not conform with the general conception of true diabetes insipidus However the anatomical involvement of the pituitary stalk as well as the hypothalamic region with xanthomatous granuloma is sufficient proof that one has to deal with a real diabetes insipidus rather than with nervous polydipsia and nervous polyuria These symptoms sometimes may subside temporarily and then reappear

Endocrine Symptoms—Other endocrine symptoms are usually also the result of the involvement of the pituitary gland and subthalamic region A retardation of growth is frequently observed In some cases there may be a considerable loss of weight and emaciation in others a rapid gain in weight with features of obesity is noted These features probably are due to the involvement of the subthalamic region In rare cases not only diabetes insipidus but also diabetes mellitus is observed (see Case XL) These endocrine features may occur only temporarily

Nervous System Symptoms—Cases XLI and XLII had epileptic seizures which are significant of a lesion in the parietal lobe and the middle cranial fossa There were no tumor symptoms such as increased pressure headaches or vomiting In Case XLII the protein content of the lumbar fluid was elevated Operation does not seem advisable in these instances because of the diffuse nature of the anatomical lesion

Thannhauser and Magendantz found symptoms of a disturbance of the automatic mechanism of the urinary bladder in two cases Ischuria paradoxa was observed in these patients This kind of disturbance probably is the result of the involvement of the automatic centers of the bladder in the medulla The editor (H A C) in 1932 saw in the office of Dr W H Bunn of Youngstown Ohio a girl of 10 years a patient of Dr J E L Keyes with typical facial appearance bone defects and polyuria who had spastic paraplegia This patient now (1940) is 18 years old emotionally unstable with polydipsia and polyuria subnormal central vision and spastic paraplegia (letter from Dr Bunn)

A case described by van Bogaert[8] apparently does not belong to

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Mastoid and Sinuses—Some cases have been reported in which there

which it may be confused However if osteolytic bone lesions are the only manifestation of the disease differentiation from other osteolytic lesions may be difficult

In Gaucher s disease osteolytic lesions of cyst like appearance are rarely found The x ray features of Gaucher s disease are rarefaction of the bone due to diffuse replacement of the bony structure by Gaucher s cells the mottled appearance of the bones due to hypercalcification and decalcification and most characteristic the thinning of the distal ends of the bones with flaring (Erlenmeyer s flask) of the distal ends of the long bones For a definite differential diagnosis a bone marrow biopsy must be performed

In Niemann Pick s disease visible bone changes are rare in contrast to the involvement of all organs This disease is easily distinguished from the Schuller Christian syndrome by its clinical features

Bone changes may occur in various types of lymphomas especially in Hodgkin s disease In these cases the changes sometimes may be cyst like They are mostly located in the periosteum of the phalanges of the hands and vertebrae they are never found in the calvarium

The bone changes of multiple myeloma revealed by x ray pictures have often in the past been confused with those of the Schuller Christian syndrome However in the former disease there is a prevalence of destructive processes without any reparative processes The lesions in the calvarium usually vary in size and are round in shape The presence of plasma cells in the bone marrow biopsy and the high serum proteins facilitate clinical differentiation The same diagnostic considerations hold true for the differentiation of the Schuller Christian syndrome and chloroma

In Cooley s disease the changes in the skull and bones are entirely different in appearance from those of the Schuller Christian syndrome Osteosclerotic symptoms with decalcification and hypercalcification are found in erythroblastic anemia Here again the blood picture is most decisive for making a differential diagnosis

Isolated bone cysts of unknown etiology may cause diagnostic difficulty in some instances Bone marrow punctures or biopsy are the only means of making a differential diagnosis in such cases Bone metastasis malignant tumors and irregular bone defects may in rare cases simulate Schuller Christian defects of the membranous bones of the skull The diagnosis in such cases is determined easily by the accompanying clinical symptoms

Some difficulty may arise in distinguishing histologically the Schuller

Schuller Christian syndrome (eosinophilic xanthomatous granuloma normocholesteremic xanthomatosis) because tendon xanthoma characteristic of the hypercholesteremic group of xanthomatous diseases were present Ataxia with asthenia and diffuse amyotrophia of all four limbs were the outstanding nervous symptoms in van Bogaert's case Kyphosis of the cervical and thoracic spine developed with the amyotrophia Despite the amyotrophia the tendon reflexes were increased The fine descriptions and excellent histological pictures in the report of van Bogaert and his associates[9] should be seen in the original because these findings are unique in the literature

Lung, Lymph Nodes, Spleen and Liver —The clinical triad of the symptoms complex described by Schuller and Christian does not embrace the involvement of these organs The involvement of these organs is significant of the generalized form of the disease under discussion (see Section on Generalized Form of Eosinophilic Xanthomatous Granuloma

Blood —*The production of red blood cells in the bone marrow* is not affected although mild hyperchromic anemia may develop There are no distinct signs of bone marrow insufficiency No case has been described with panmyelophthsis a condition which could result from an intensive infiltration of the bone marrow by foam cells and granulomatous scar tissue Abnormal cells which simulate foam cells erroneously designated as vacuolated agranulocytes have not been observed in the blood stream Coagulation and bleeding time of the blood are normal Fragility is not increased

Blood Chemistry —Total cholesterol is normal or a high normal There is no increase in neutral fat or other lipid substances Carotene is not increased

Urine —The specific gravity of the urine varies between 1 001 and 1 010 No sign of kidney damage is found in the urine The red and white cells occasionally found may be the result of cystitis in cases where the bladder reflex is disturbed and the bladder becomes distended

Diagnosis and Differential Diagnosis

Each of the symptoms of the Schuller Christian triad bone defects exophthalmos and diabetes insipidus may occur alone each symptom may be combined with xanthoma disseminata or all three symptoms may occur simultaneously with xanthoma disseminatum

If the entire clinical triad is developed there is no other disease with

tous lung involvement reported the following gross anatomical findings The lungs were voluminous and felt fibrous to palpation The lungs were somewhat adherent over the posterior lateral aspect of the costal pleura the adhesion being of the same peculiar yellowish gummy nature that was noted in the granuloma of the skull When the lungs were removed they were found distended and firm to the touch and on section presented a remarkable appearance The whole lung was a mass of communicating vesicular cavities These cavities varied in size from that of a pinhead to that of a large pea The septa between the cavities were fibrous and inelastic The walls of the blood vessels were somewhat thickened The general appearance suggested a low grade pulmonary hyperplasia or an intensive or diffuse form of pneumonitis with marked emphysema

Gross examination of viscera at autopsies on various cases showed the following *Pleura* Yellowish plaques on visceral and external surfaces *Lungs* Small patches of whitish or yellowish color with the appearance of leukemic infiltration are scattered through the lung tissues There may be large masses of rubbery fibrous tissue the inner surface of which shows a grayish fibrous stroma with scattered areas of yellow tissue hemorrhage and softening *Pericardium* Some yellow plaques similar to those covering the pleura may be found on the visceral pericardium The endocardium and the valves are not involved (in contrast to familial hypercholesteremic xanthomatoses) *Spleen and Lymph Nodes* The enlarged organs show on section scattered grayish yellow spots of various sizes *Liver* The structure of the liver is not grossly disturbed The liver is not cirrhotic in any phase of the disease but on section is speckled with small grayish white patches like the spleen These findings are entirely different from those of xanthomatous biliary cirrhosis (pericholangiolitic cirrhosis) where patchy infiltrations are absent but in the final stage the structure of the whole organ is grossly disturbed by fibrous cirrhotic strands *Bone Marrow* Grayish yellow irregular softened areas are interspersed in the normal marrow

Histology —The lesions of different organs show various phases of development Holm Teilum and Christensen distinguished four stages (1) a hyperplastic proliferative phase (2) a granulomatous phase (3) a xanthomatous phase (4) a fibrous phase (discussion see Histology in this section) In the various organs involved in the generalized form of eosinophilic xanthomatous granuloma these different phases overlap considerably One lesion may show hyperplastic reticulo endothelial proliferation another may be characterized by the eosinophilic and granu

Christian syndrome from osteitis cystica localisata et disseminata (fibrous dysplasia) because bone biopsies show that in some areas of the fibrous lesion in osteitis cystica disseminata scattered foam cells may be present. The histological structure in this fibrotic growth is entirely different from the lesion in the Schuller-Christian syndrome. The latter, even in its fibrotic phase, reveals cellular elements of a granuloma while in osteitis fibrosa cystica the lesion is wholly formed by fibroblasts in pallisades or fibroblasts in whorling arrangement. Cafe au lait spots and severe bone deformities characteristic of this disease are not observed in the Schuller-Christian syndrome.

5 Generalized Form of Eosinophilic Xanthomatous Granuloma (Generalized Lipid Granulomatosis, Generalized Xanthomatosis of the Normocholesteremic Type, Generalized Form of Schuller Christian Syndrome Acute Reticulo-endotheliosis)

Hand[3] [37] Pusey and Johnstone Turner, Davidson and White[10], Thompson Keegan and Dunn[99] and Letterer[4] described cases with the most extensive manifestations of eosinophilic xanthomatous granuloma (xanthomatosis of the normocholesteremic type) with involvement of the bones lungs and lymph nodes. Small pinhead xanthomatous lesions were found in almost every organ where reticulum cells and histiocytes are physiologically present.

Lesions may occur in the skin as disseminated xanthoma and "petechiae like lesions in bones brain and lungs on serous surfaces like the pleura, peritoneum and pericardium, in the liver and spleen and especially in the lymph nodes. Xanthomatous lesions are found even in the stomach and intestines. They are grayish-yellow and usually of the same size as the nodules of miliary tuberculosis.

Morbid Anatomy and Histology Relation to Letterer Siwe's Disease

Autopsies of infants establishing the generalized form of the disease under discussion were described by Rowland[81], Chester[11] Henschen[40], Letterer[51], Jghenti[46], Atkinson[3] Baggenstoss Rosenberg and Osterberg[7], Freud, Grossman and Draguisky[3]

Rowland[81] publishing the first anatomical description of xanthoma-

tous lung involvement reported the following gross anatomical findings The lungs were voluminous and felt fibrous to palpation The lungs were somewhat adherent over the posterior lateral aspect of the costal pleura the adhesion being of the same peculiar yellowish gummy nature that was noted in the granuloma of the skull When the lungs were removed they were found distended and firm to the touch and on section presented a remarkable appearance The whole lung was a mass of communicating vesicular cavities These cavities varied in size from that of a pinhead to that of a large pea The septa between the cavities were fibrous and inelastic The walls of the blood vessels were somewhat thickened The general appearance suggested a low grade pulmonary hyperplasia or an intensive or diffuse form of pneumonitis with marked emphysema

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lomatous phase with giant cells while in a third area the xanthomatous phase is in full development In infants however where the disease terminates rapidly in death, the reticulo endothelial phase may persist and give the impression of a diffuse reticulo-endotheliosis Such cases were described by Letterer, Siwe Abt, Gross and Jacox[31] as well as by others The prevalent opinion[81, 8, 9, 1, 31] is that the diffuse acute reticulo-endotheliosis (Letterer-Siwe disease) probably is the first phase of the generalized form of eosinophilic xanthomatous granuloma (lipid granulomatosis Schuller-Christian syndrome) The rapid termination of the disease because of an early death prevents the development of the granulomatous and xanthomatous phases observed in eosinophilic xanthomatous granuloma This favored conception of the relation between the two syndromes apparently is correct, since cases of acute reticulo endotheliosis were observed in which the xanthomatous transformation had already started[31, 34, 3, 4, 9] The designation of acute reticulo endotheliosis (Letterer-Siwe's disease) should be maintained for such cases where the reticulo endothelial phase is terminated in its development by a most rapid and fatal course of the disease and anatomical as well as chemical examination does not show cholesterol accumulation in the involved cells

Clinical Course

The beginning of the clinical course does not differ from that described in cases of other osseous xanthomas with diabetes insipidus and exophthalmos Schuller Christian syndrome However as soon as the lungs become involved the clinical picture takes a turn for the worse

Cases

Mild Form of Systemic Eosinophilic Xanthomatous Granuloma

Case XVIII —J K a five year old well developed and intelligent boy was referred by Dr D J Davies Hartsdale New York When the child was six months old the mother had noticed small colorless and later deep yellow lesions on his forehead These skin lesions gradually spread over his face neck trunk elbows and legs (Fig 91) There were none on the palms or soles In addition to the typical xanthoma disseminata in lines and clusters there were pea sized solitary papules described as juvenile xanthoma (see Fig 91) This simultaneous occurrence of these two types of lesions confirms the author's opinion that both lesions are intimately related

7 - 46 When he was first examined in our hospital these eruptions



Fig 91 Disseminated xanthoma skin lesions of eosinophilic xanthomatous granuloma (case XLIII)

were yellowish tan and numerous all over the body arranged singly or grouped in ridges and were most marked in the skin folds The physical examination otherwise was negative There was no exophthalmos no polyuria Urine showed specific gravity 1 0 0 Liver and spleen were normal in size X rays of lungs and osseous system were negative Since there was a suspicion of slight glycosuria by the attending physician when the child was 13 months old a glucose tolerance test was carried out Fasting blood sugar was 71 mgm per cent blood sugar curve was normal Blood lipids were total cholesterol 167 mgm per cent free cholesterol 55 mgm per cent cholesterol present as esters 11 mgm per cent (66 per cent of total cholesterol) Serum was clear and transparent

3 - 46 Diffuse adenopathy in neck axilla and groin Spleen is slightly enlarged The boy gives the impression of being a healthy child The skin xanthoma are unchanged Laboratory findings are hemoglobin 78 per cent cholesterol present as esters 112 mgm per cent (66 per cent of total tial count is normal Fasting blood sugar is 65 mgm per cent Urine shows specific gravity 1 020 Total cholesterol is 170 mgm per cent free cholesterol 25 mgm per cent cholesterol present as esters 145 mgm per cent (85 per cent of total cholesterol)

3 15 47 The general condition of the child is very good He has grown normally and gained weight The skin xanthoma are as numerous as last year but lighter in color The enlargement of the lymph nodes has not changed The size of the spleen also is the same Lungs are normal by x ray but x ray of the bones shows a definite oval lesion on the lower end of the right femur

Biopsy of Inguinal Lymph Node 5 13 46—The follicles are normal in size The pulp cords show accumulation of reticulum cells No foam cells are present There are recent hemorrhages in some areas of the glands Diagnosis Reticular proliferation with hemorrhages

Biopsy of Skin 10 31 46—Dr Heffering pathologist at the White Plains Hospital New York reported the histology of early yellowish skin lesions of the disseminated type as follows Beneath a regular squamous surface of epithelium cells are irregular congeries of small blood vessels of capillary size They are lined by a single layer of regular endothelial cells The large number of vessels is well brought out with the Wilder stain Around each of them is a delicate basement membrane of reticulum and from this there extend outward concentric strands of similar reticulum In the meshes of this network are large pale staining cells with a fine foamy cytoplasm and ovoid small vesicular nucleus Eosinophiles are not present in large numbers

Biopsy of Skin 9 -3 47—The epithelium varies a little in thickness but it has the usual architecture The basal layer is deeply pigmented with melanin Beginning immediately beneath the epithelium and extending down through the corium are loosely disposed small groups of tiny capil-

laries accompanied by plump large mononuclear cells and an occasional lymphocyte. The endothelial cells of the capillaries are somewhat swollen. The mononuclear elements tend to have a pale staining finely vacuolated cytoplasm enclosing an ovoid diffusely staining nucleus. Frequently these cells appear to have coalesced giving rise to small multinucleated cells with from 3 to 6 peripherally placed nuclei enclosing both foamy and more solid eosinophilic cytoplasm. These vessels and cells are loosely distributed in the collagen of the corium and the collagen in turn runs quite irregularly in all directions. No discrete tumor nodule is present, the lesion being essentially a vascularization of the corium accompanied by the cells described. The foamy cells which could not be identified in the first biopsy because of lack of material now prove to be laden with lipid. Scharlach R stain brings out a large amount of well stained lipid occurring in small droplets mainly in the cytoplasm of mononuclear cells and sometimes in spindle shaped cells. A little lipid appears to be present outside of cells as well.

Case XVII.—H. S., a five-year old white boy, whose case is reported by Rowland[141] had no family history of xanthomatoses. Development was normal. His first teeth appeared when he was six months old. At ten months he weighed twenty-six pounds. He had a small abscess on his skull at eleven months and otitis at twelve months. After a mild attack of measles when he was two years old the patient did not appear as well as usual. Six months later his tonsils were removed. A soft swollen area which was found on the back of his head at this time was thought to have been the probable result of a fall down some steps. A physician was not consulted until the child was three years and nine months old. At this time another swelling and soft spot appeared in the right temporal region. The mother attributed this to the child's striking his head against the corner of a table.

Examination at this time showed a marked degree of exophthalmos and strabismus. The vision and the eyegrounds were normal. The alveolar processes were swollen and tender. Most of the teeth were loose and infected, producing a foul odor of the breath. He had already lost a number of teeth, ten having been extracted at one time. There was a slight serous discharge from both ears with questionable mastoid tenderness.

Physical examination revealed that the boy was considerably undersized for his age. He was fairly well nourished and did not show abnormal deposits of fat. He was pale, cyanotic and dyspneic. The patient weighed twenty-nine pounds (13.2 Kg.) and was 38 inches (96 cm.) tall. The temperature was 100.4 F. The respiratory rate was 3_. The skin was not especially dry and did not show any eruptions. The glands in the posterior cervical region were the size of shot. Other glands were not enlarged. The head, which was large in proportion to the body, was 50 cm. in circumference. The face was oval. There was a normal amount of brown hair. A noticeable bulge was present in the frontal region in an area 5 by 7 cm.

in which there was an absence of bone This area protruded when there was a straining as in coughing or crying and pulsation would be felt Most of the bony edge was sharply defined There was a similar area in the right temporal region 4 5 by 3 5 cm and a smaller area in the left parietal region irregularly outlined 2 cm in diameter At other points the surface was slightly elevated as in the frontal region

The eyes showed marked exophthalmos which was greater in the right The right eye turned downward and inward The pupils were slightly dilated regular and equal They reacted to light and accommodation The muscle response was normal and nystagmus was not present The fundi appeared normal the disks were well defined and the vessels were normal in size and appearance

There was a thin purulent discharge from both ears more from the right Both tympanic membranes were partially destroyed The bridge of the nose had a sunken appearance which was probably due to a bulge in the frontal region The nasal passages were small due to evident swellings of the mucous membrane The breath was foul The alveolar arches were irregular and swollen and bled easily Only three teeth remained they were the lower incisors and were loose and covered with a tartar like substance Tenderness and swelling were present over the maxillæ which added to the fullness of the lower portion of the face The tongue was heavily coated a light brown The throat was congested and a dull red with a thick purulent mucus dropping from the posterior pharynx There was no evidence of tonsillar tissue The thyroid was not palpable

The heart showed a maximum impulse in the fifth inter space 1 cm outside the nipple line The sounds were clear and distinct Murmurs were not heard The pulse was small and easily compressible with the rate of 1 6 Blood pressure was 80/40 The lungs were slightly hyperresonant throughout The breath sounds were loud and distinct without prolongation of expiration Occasional coarse rales were heard in both bases The abdomen was moderately distended but not tender The spleen was not felt and the area was not increased to percussion The edge of the liver was felt 3 cm below the costal margin in the mammary line The genitals were well developed and normal The spine showed slight prominence of the last dorsal vertebra The muscles of the extremities were small and flabby The hands and feet were normal in size and proportion There was no clubbing of finger tips There was slight edema of the lower extremities The knee reflexes were not exaggerated and were equal The Babinski Kernig or Brudzinski signs were not elicited The plantar reflexes were normal

X ray examination showed multiple defects on both tables of the skull The process involved especially the frontal and parietal as well as the occipital bones with the greater destruction in the frontal bone

By December 19 5 the patient had grown progressively weaker He

complained occasionally of pain in the right side His cough was more distressing Cyanosis and dyspnea were extreme He was unable to sleep except when propped up in bed He had no appetite and refused even fluids He was almost continuously nauseated and vomited several times The heart action was rapid with a rate of 148 The pulse was small and easily compressible No apex impulse was felt the sounds were faint The blood pressure was 70/30 Edema of the dependent parts had increased The boy was not thirsty and passed little urine

The boy was removed to the hospital where he failed rapidly and died on January - 19 6 The fatal termination was attributed to cardiac failure due to impaired circulation resulting from extensive pulmonary fibrosis

The following case is a most typical example of the generalized fatal form of eosinophilic xanthomatous granuloma in an infant It is reported by Paul Freud Leo Grossman and David Dragutsky in an article entitled Acute Idiopathic Cholesterol Granulomatosis [8]

Case XLIV M J a 7 month old boy weighed 5½ pounds (495) at birth Both parents were Swedish of unrelated stock The patient s growth and development had been normal up to the present illness The family history was noncontributory

The child became ill with a sore throat Two days later the mother noted bilateral glandular swelling in the neck and within a week similar swellings were seen in the axillas and groins The baby was seen approximately two weeks later by one of us (P F) There was generalized lymph adenopathy and severe secondary anemia was demonstrated by an erythrocyte count of 700 000 cells per cubic millimeter and a hemoglobin content of 7 per cent (Sahli) the white blood cells numbered 4 100 per cubic millimeter A tentative diagnosis of aleukemic leukemia Hodgkin s disease or lymphosarcoma was made

The patient was transferred to the Metropolitan Hospital where the following observations were made The child was extremely pale and apathetic His temperature was 100 F his pulse rate was 100 and his respiratory rate 6 and he weighed 4- pounds (10 9 Kg) Serous nasal discharge was present The left ear drum was injected There was loss of the normal shape of the neck because of the marked enlargements of the cervical lymph nodes The nodes on the left side were soft and their centers fluctuant and the overlying skin was slightly reddened

There was impaired resonance on percussion but no diminution of breath sounds was present over the upper part of the left side of the chest anteriorly The heart was enlarged a blowing systolic murmur was heard over the apex and a distinct friction rub at the base Abdominal distention was present but the liver and spleen were not palpable Discrete soft non tender nonfluctuant lymph nodes ranging in size from that of a pea to that of a plum were easily seen and palpated in the axillas and groins

TABLE XXIX

Results of Blood and Bone Marrow Counts

Date 1940	Hemoglobin content (Sahli) per Cent	Red Cells	White Cell	Results of Differential Count per Cent		Comment
April 12	27	2 720 000	6 900	Polymorphonuclears (Band 8)	80	
				Lymphocytes	14	
				Eosinophils	2	
				Monocytes	4	
April 13	36	2 80 000	4,400	Polymorphonuclears (Band 11)	67	Platelets 350,000
				Lymphocytes	22	
				Monocytes	9	
				Eosinophils	2	
April 20	Total marrow count		40 000	Promyelocytes	2	Sternal marrow was examined a transfusion was given on April 1
				Neutrophilic myelocytes	9	
				Eosinophilic myelocytes	1	
				Metamyelocytes	23	
				Stab cells	0	
				Segmented cells	3	
				Lymphocytes	10	
				Monocytes	1	
				Eosinophils		
				Normoblasts 4 per 00 white blood cells		
May 5	41	2 370 000	7,400	Polymorphonuclears (Band 1)	78	
				Lymphocytes	3	
				Monocytes	5	
				Eosinophils	1	
May 18		2,400 000	6 000	Polymorphonuclears	41	Platelets ,8 000 bleeding time 2 min coagulation time 4 min a transfusion was given on May 18
				Lymphocytes	56	
				Monocytes	2	
				Eosinophils	1	
May 21	58					

One hundred per cent is represented by 14 5 Gm

Study of the bone marrow (Table XXIX) demonstrated nothing unusual. The microscopic diagnosis made on one of the glands was lipoid histiocytosis. Roentgenograms of the chest showed clouding of the upper lobe of the left lung while studies of the long bones and the skull showed no bone defects or other abnormalities.

Course—From May 2 the patient's course was rapidly downhill. Bilateral otitis media developed and necessitated myringotomy. All of the lymph nodes became larger and appeared doughy. The cervical glands on the left side became matted together and the occipital glands became palpable for the first time. The left side of the chest was dull to percussion and bronchial breathing was heard throughout. The cardiac apex, however, remained unshifted. Roentgen study showed dense clouding of the left side of the chest. For laboratory findings see Table XXX.

TABLE XXX

Laboratory Findings

Constituents of blood, mg per 100 c c	
Dextrose	94
Nonprotein nitrogen	20
Calcium	9
Phosphorus	3 6
Total cholesterol	134
Free cholesterol	44
Cholesterol esters	90
Lecithin	140
Neutral fat	150
Total lipids	4 0
Phosphatase units per 100 c c	6 8
Concentration of plasma proteins, Gm per cent	3 77
Albumin	2 50
Globulin	0 9
Fibrin	0 35
Carbon dioxide combining power of blood, volumes per cent	45
Icteric index	5 7
Van den Bergh reaction	Negative
Reaction to heterophil antibody test (Paul Bunnell)	Negative
Reaction to Mantoux tests (with dilutions of old tuberculin up to 1 100)	Negative
Reaction to Wassermann, Kahn and Kline tests	Negative
Blood typing (international)	0
Results of examinations of spinal fluid (May 15 and June 4)	Normal
Result of gastric analysis (May 17)	No free hydrochloric acid, low *total acidity*

On May 3 the weight was 16 pounds 9 ounces (7 5 kg) the temperature varied from 100 to 103 F and petechiae varying in size from that of a millet seed to mm in diameter were seen on the trunk The contour of the chest became distorted because of the bulging cartilaginous portions of the upper ribs on the left side parasternally Percussion over this area produced vibrations which persisted for a few seconds and were similar to those produced by thumping of a tight drum Tubular breathing now appeared also over the lower lobe of the right lung Roentgenograms of the long bones and the skull showed no changes There was some clouding over the base of the lower lobe of the right lung A second biopsy of an enlarged inguinal lymph node was performed and again the diagnosis of lipoid histiocytosis was made Chemical quantitative study of the tissue demonstrated 12 6 mg of total cholesterol per cent of dry weight consisting of 0 7 mg of free cholesterol and 11 9 of cholesterol esters (see Table XXXI)

TABLE XXXI

Lipoid Content of the Tissue

	Normal Spleen or Lymph Node	Spleen or Lymph Node in Cases of Schüller Christian Disease	Lymph Node (Biopsy) in Our Case	Retrosternal Mass (Necropsy) in Our Case
Kerasin	0	0	0	0
Free cholesterol	0 6	Up to 3	0 7	
Cholesterol esters	0 87	Up to 1[illegible] 3	11.9	15 7
Total cholesterol	0 9	Up to 18 58	12 6	1[illegible] 9
Lecithin	1.66	Up to [illegible]1.78	8	Trace
Neutral fats	4 2	Up to 14.4	4 8	
Total lipoids	4 6	Up to 34.66	19.6	
Total fatty acids	8.0			8.0
Total phospholipids	4.0			6.4
Sphingomyelin	1.0			Trace
Cephalin	2 5			6.4

The values are expressed as percentages of the dry weight of the tissues

In the last week of life the course of the illness seemed almost malignant The child was extremely pale and there were rapid grunting respirations and temperature ranging from 10 to 104 F The petechiae increased in number and size (Remark of author probably petechiae like lesions of the skin due to reticuloendothelial proliferation around a capillary)

On June 4 there was an icteric tint to the skin and paralysis of the left facial nerve of peripheral type developed Showers of petechiae appeared

on the scalp There were signs of meningeal irritation, but examination of the spinal fluid gave negative results Death occurred that evening

Biopsy —Examination of an inguinal lymph node showed that the tissue was almost completely replaced by large pale staining reticuloendothelial cells These cells were closely packed together and had moderate sized vesicular nuclei and indistinct amounts of cytoplasm which showed reticulation and vacuolation There were moderate numbers of multinucleated giant cells The primary lymph follicles were absent and the lymph cords were small and compact The peripheral sinus and the medullary sinusoids were almost completely obliterated by the reticuloendothelial cells There were small areas of hemorrhage but no focal necrosis There was only slight fibrosis in the hilar region Sections prepared with nile blue sulfate and the Smith Dietrich stain showed a high lipoid content

Autopsy —The histology of lungs lymph nodes liver, spleen and a retrosternal mass are described in the original paper The histological findings of the lungs which showed similarity to other involved organs were as follows

Lungs Sections of the periphery of the lung showed no sharp demarcation between the proliferating fibroblastic and cellular tissues of the retrosternal mass and the pleural and subpleural structures Columns of fibroblastic tissue in which there were numerous histiocytes extended deeply into the lung along the planes of the interlobular septums Many of the alveoli were collapsed or contained numerous mononucleated macrophages with vacuolated cytoplasm In some foci the alveolar tissues were replaced by large nodular infiltrations of lymphocytes macrophages and few multinucleated giant cells In other foci groups of alveoli were filled with a coarse fibrinous material in which macrophages and a few lymphocytes were embedded

Sections of the periphery of the lung stained with scarlet red showed that many of the macrophages in the alveoli contained numerous small globules of lipoid material Sections of deeper lying structures showed an increase in the interstitial tissues particularly about the blood vessels and the medium sized bronchi Around some of the bronchi there was some very cellular connective tissue in which histiocytes fibroblasts giant cells lymphocytes and a few eosinophils could be recognized The tissue compressed the bronchus so that its lumen was narrowed and its lining epithelium was thrown into large folds

Terminal bronchi were filled with polynuclear cells and infiltration with lymphocytes and mononuclear and polynuclear cells was observed in their walls extending outward into the interstitial tissue between the alveoli These lesions resembled those of interstitial bronchopneumonia Foci of emphysema and of alveolar edema were noted

The chemical analysis of the lymph node (see Table XXXI) demon

strated the enormous (17 times that of normal) accumulation of cholesterols in the cells while the total cholesterols in the serum were normal Similar chemical findings of skin liver and lymph nodes in our laboratory are discussed in section on pathogenesis of xanthoma formation The chemical findings of normal serum cholesterol and high tissue cholesterol in respect to foam cell formation in eosinophilic xanthomatous granuloma can only be interpreted on the basis of an increased cholesterol formation within certain cells of the examined tissue and not by cholesterol infiltration and deposition of cholesterol from the blood stream

Clinical Features

Age —The generalized form of eosinophilic xanthomatous granuloma (lipid granulomatosis lipid histiocytosis generalized form of essential xanthomatosis of the normocholesteremic type acute idiopathic cholesterol granulomatosis) occurs mainly in infants Observations showing involvement of lymph nodes liver and spleen in adults are very rare

Brain Involvement, Diabetes Insipidus and Exophthalmos —In the generalized infantile form involvement of the brain exophthalmos and diabetes insipidus are not reported The involvement of the brain resulting in the classical triad of Schuller Christian syndrome apparently has not yet fully developed in these infantile cases There seems however little doubt that detailed histological examination of the brain will reveal also incipient lesions namely histological perivascular infiltrates as described in adults by Teilum[93]

Skin —Xanthoma of the disseminata type and especially the petechiae like lesions of the skin characteristic of eosinophilic xanthomatosis are observed in the generalized form of the disease[51]

Bones —X rays of the case of M Freund and M Ripps[9] already showed involvement of the bones when the child was fourteen months old Usually the bone marrow lesions in infantile cases of the generalized form of Schuller Christian disease are found only by histological examination at autopsy[51,7]

Lungs —The patient develops a cough and bronchitis which are followed later by fever Signs of lung infiltration such as lung dullness develop Moist consonant rales are heard over these parts The dullness usually persists after the disappearance of the fever At the same time a slight cyanosis appears The patient s breath becomes shorter and respiration is difficult The cyanosis increases even with slight exertion The signs of circulatory failure due to the insufficiency of the lesser circu

lition become increasingly prominent and result in the death of the cyanotic patient It is evident that the small patchy, bronchial pneumonic infiltration of the lung with xanthomatous granuloma tissue results in fibrosis of the lung

The picture is that of chronic pulmonary fibrosis which causes in its course failure of the lesser circulation with cyanosis Diffuse bilateral fibrosis is revealed by the x ray of the lungs In some places the lung has a mottled appearance, resembling that in miliary tuberculosis (Fig 92) However, the size of nodules in the lung is not uniform They



Fig 92 X ray picture of xanthomatous involvement of the lung case XLIV Note the fine nodules simulating miliary tuberculosis (Rowland[344])

are partly larger and partly smaller The x-ray picture is very similar to that of pneumonoconiosis found in occupational lung diseases resulting in fibrosis

Lymph Nodes—Axillary submaxillary and inguinal lymph nodes are increased in size They are not tender but firm Biopsy and chemical analysis are discussed in description of Cases XLIII and XLIV

The lymph nodes in some cases are so enlarged that the aspect of the patient is similar to that seen in cases of Hodgkin's disease

Spleen and Liver—Only 8 of the 26 cases of the Schuller-Christian syndrome mentioned by Rowland showed enlarged spleen or liver In 7

of these cases the enlargement of the organs was never outstanding and even doubtful Jaundice is not found in cases of the generalized form of the Schuller Christian syndrome even if the liver is enlarged because the lesions are only scattered through the liver without causing destruction of the organ structure or producing biliary cirrhosis The scattered lesions in the liver are identical with those in the spleen and lymph nodes They are discretely interspersed in the tissue like the nodes of miliary tuberculosis No impairment of the liver is revealed by function tests

In rare cases the only organs involved may be the lymph nodes liver spleen and lungs without involvement of the skin and bones Since these cases exhibit normal cholesterol values only chemical analysis and biopsy of the organs can reveal the diagnosis

There is one case described by M L Dreyfuss and E H Fishberg[18] where only the spleen and lymph nodes were enlarged The spleen showed nests of foam cells Since the cholesterol in the serum was normal in contrast to the enormous increase of cholesterol in the spleen this case also belongs to this group

Blood —Anemia thrombocytopenia and low leucocytes (pancytopenia) (see Case XLIV) may be found in some infantile cases of the generalized form of eosinophilic xanthomatous granuloma Pulmonary involvement manifesting itself as pneumonitis or fibrosis may cause higher numbers of leucocytes

Serum —The figures for serum lipids cholesterols phospholipids and neutral fat are normal The serum is transparent and not lipemic Bilirubin and icteric index are normal even in cases where the liver is enlarged

Differential Diagnosis

The generalized form of eosinophilic xanthomatous granuloma in infants is clinically distinguished from the infantile form of Gaucher's disease by the absence of cerebral manifestations rigidity of legs and limbs and laryngeal spasms characteristic symptoms of infantile Gaucher's disease

The clinical characteristics of Niemann Pick's disease like general cachexia and rapidly progressing physical and mental debility are not present in the generalized infantile form of eosinophilic xanthomatous granuloma If one wishes to maintain acute reticulo-endotheliosis (Letterer Siwe's disease) as a disease entity different from the acute infantile

form of eosinophilic xanthomatous granuloma, the differential diagnosis can only be made by histological examination of a biopsy of a lymph node. The definite differential diagnosis also in the aforementioned infantile forms of Gaucher's and Niemann-Pick's diseases should be verified by biopsies.

Skin manifestations of eosinophilic xanthomatous granuloma, if present, are a great help in differential diagnosis. Xanthoma of the disseminated type and especially the "petechiae-like lesions" around the capillaries are pathognomonic of the infantile form of the disease under discussion. In the infantile form of Gaucher's disease skin manifestations or pigmentations are not observed. In Niemann-Pick's disease a diffuse yellowish-brown discoloration of the skin may be present. X-ray of the lung is not helpful in differential diagnosis, since in all three infantile forms of these disorders the lung is involved and similar x-ray pictures of the organs may result.

The generalized form of eosinophilic xanthomatous granuloma in adults is extremely rare since most of the infants and children exhibiting the generalized form of the disease pass away after a rapid course of the disease.

Addendum

There are three cases in the literature which are hard to classify. These cases are reported by the following authors:

(1) Hardaway[38] (1890), ( ) Weidman and Freeman[10] (19 4), Griffith (19-2) (case is identical with Weidman and Freeman's[10]), (3) Weidman and Stokes[104] (19,7), Gitting[30] (1928) (case is identical with that of Weidman and Stokes[108]).

Hardaway's[38] patient exhibited xanthoma disseminatum of face, neck, axillae, trunk, extremities and mucous membranes of the mouth and larynx, osseous xanthomata of the long bones, xanthomatous lesions in a herpes zoster, hepatic cirrhosis with jaundice and xanthoma of the tendons. Hardaway spoke of an xanthomatous diathesis. He suggested like Quinquard[73] (1879) who had used the expression "diathese xanthomatique" that xanthoma affection is a "diathetic affection" and that its connection with hepatic disease is only secondary, that is, jaundice occurring during the course of the disease is a consequence of a deposition of xanthomatous tubercles in the liver.

Weidman and Freeman[10] reported the case of a nine year old boy who exhibited, like Hardaway's patient, xanthoma disseminata and xan-

thoma planum which are described by the authors as hundreds of little nodules in the mouth neck axillae elbows knees also in the lines of the palms The margins of all four lids had long flat lesions There were several nodules on the side of the head the underlying bones were depressed and roentgenograms showed small bony defects of the frontal and parietal regions The boy was jaundiced polyuric (diabetes insipidus) and had an enlarged liver Total cholesterol 397 mgm per cent The post mortem revealed xanthomatous involvement of the skin brain pituitary and tuber cinereum diffuse xanthomatosis of the lung xanthomatous biliary cirrhosis xanthomatous changes in the lymph nodes xanthoma of the dura and skull

Weidman and Stokes[109] reported the case of a six year old girl with tuberous xanthoma in operative scars apparently the eruptive form of xanthoma associated with a very high blood cholesterol (1 039 mgm per cent) in 1928 Gitting[3] had reported the same case with a blood cholesterol of 1 0 mgm per cent The child also had diabetes insipidus but no exophthalmos The roentgenogram did not show skull involvement Xanthoma were found at the roots of the teeth There were also jaundice and an enlarged liver There was no autopsy

In the first edition of this chapter these cases were considered as essential xanthomatosis of the combined type since xanthoma disseminata of the skin and brain lesions diabetes insipidus and bone lesions belonging to the normocholesteremic group (eosinophilic xanthomatous granuloma) and jaundice and biliary cirrhosis significant of the hypercholesteremic group were present together The reported values for serum cholesterol in these cases are not reliable for differential diagnosis since the methods for cholesterol determination at this time were not precise enough

The present opinion of the author is that one is not justified in assuming the existence of a combined type i e that the features of eosinophilic xanthomatous granuloma (normocholesteremic xanthomatosis Schuller Christian syndrome) occur in one patient together with the features of hypercholesteremic xanthomatosis since both disease entities are entirely different in their pathogenesis The classification of cases as xanthomatous diseases of the combined type must be abandoned It seems preferable to leave the classification of these three cases open until similar ones may be encountered and examined at different stages of the disease with more detailed chemical and histological methods

Prognosis

The generalized form of eosinophilic xanthomatous granuloma (acute reticuloendotheliosis) occurring in infancy is a fatal disease. The few cases of the generalized form observed in adult life were probably at the beginning not generalized and the disease progressed later with involvement of the lungs, liver and spleen.

The prognosis in eosinophilic xanthomatous granuloma is entirely different if the first symptoms of the disease manifest themselves in the patient's later life. The older the person, the more favorable is the prognosis concerning the life expectancy. If the disease remains confined to the skin and osseous system or even to the classical triad of the Schuller Christian syndrome, the prognosis is not too unfavorable[81,82]. The generalization of the disease with involvement of lungs, liver and spleen immediately changes the prognosis in infancy as well as in later life.

Treatment

Since eosinophilic xanthomatous granuloma (essential xanthomatosis of the 'normocholesteremic type' lipid granulomatosis) is a granulomatous disease in which reticulum cells and histiocytes develop into xanthoma cells because of an increased intracellular synthesis of cholesterol, the reduction of cholesterol and fat in the diet cannot be expected to be of great benefit as it is in the 'hypercholesteremic xanthomatoses' or in eruptive xanthoma due to hyperlipemia. Slight restriction of foods containing animal cholesterol may be considered to reduce the exogenous quota of cholesterol, but strict diets free of animal cholesterol and low in fats do not influence the progress of the reticuloendothelial stage to its xanthomatous phase.

X-ray treatment of the bone lesions, especially of the membranous bones and skull, has been successful in some cases as shown by Sosman[87,89] and others. The same holds true for x-ray treatment of the enlarged lymph nodes. No success has been noted in the x-ray treatment of lesions of the skin and viscera.

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June 1 1949

B XANTHOMA CELLS IN INFLAMMATORY TISSUE AND IN TRUE TUMORS

Pathogenesis of Xanthoma Cells in Inflammatory Tissue

Xanthoma cells may originate in an inflammatory, fibromatous, sarcomatous or carcinomatous tissue Pick and Pinkus[40] as well as Kirch[4] [6] state that endothelial reticular, histiocytic, advential and in rare instances, epithelial cells may develop into xanthoma cells As the number of cells undergoing such changes increases, the tumor becomes more yellowish and appears as a xanthomatous tumor According to Pick and Pinkus[40] a true blastoma is formed not only from xanthoma cells

This author however, does not concur with Pick and Pinkus[40] and Kirch[4] [5] [6] in their explanation of the cause of the metamorphosis of the reticular and histiocytic cells into foam cells in inflammatory fibrotic and tumorous tissue These investigators believe that the retention of cholesterol within these cells is the result of a prior increase of blood cholesterol which is taken up from the blood stream and absorbed and retained within these cells (cholesterol infiltration) Contrary to this conception the author would prefer to explain the pathogenesis of xanthoma cells in inflammatory and tumorous tissue in the same way that he has suggested for the origin of xanthomatous cells in eosinophilic xanthomatous granuloma The foam cells are the result of an intracellular process particularly in histiocytes and reticulum cells which leads to an accumulation of cholesterol and cholesterol esters within the cell regardless of the level of the blood cholesterol

The xanthoma cells originate in inflammatory and tumor tissue in a single tumor while the foam cells in eosinophilic xanthomatous granuloma develop wherever lesions of this systemic disease are found in the organism The fact that the level of serum cholesterol is normal in both instances is in favor of the suggested *explanation rather than the theory* of cholesterol infiltration Since hyperlipemia and a milky serum, which are the prerequisite for cholesterol infiltration into the cells are never observed in these cases xanthoma cell formation in inflammatory tissue and in solitary tumors should be considered an intracellular enzymotic process within reticulum cells and histiocytes resulting in increased cholesterol formation and retention within the cells as suggested for eosinophilic xanthomatous granuloma

Some pathologists have ventured the hypothesis that xanthoma cell formation in inflammatory tissue as well as in tumor tissue is due to phagocytosis of cholesterol and fat derived from local cell detritus. It must be admitted that foam cells may originate occasionally as the result of phagocytosis in areas of cell destruction and necrosis. However it is not the rule to find foam cells in inflammatory or tumor tissue in areas of intensive cell necrosis.

1. Xanthoma Cells in Inflammatory Tissue

(a) Inflamed Tissue Showing Xanthoma Cells

Foam cells may appear scattered among lymphocytes, plasma cells and polynuclear cells in tissue of chronic inflammatory processes, especially in chronic osteomyelitis. Xanthoma cell formation is seen in the wall of a chronically inflamed gall bladder (so called strawberry gall bladder) and in the walls of old abscesses. It has been reported also in chronic salpingitis, in scars of different etiology and even in pock marks. Inflammatory well defined xanthomas are found in tissues rich in fat, like the breast, in the mesentery and in fat bodies of the joints.

(b) Inflammatory Xanthoma of the Breast

Hedinger[19], Müller[7] and Lobeck[21] described cases of xanthomatous degeneration of breast abscesses. Haagensen[4] also reported a similar condition which he attributed to trauma, traumatic fat necrosis of the breast. This author also described a primary xanthoma of the breast, benign tumor, which is histologically not different from the breast xanthoma due to inflammation and trauma (Fig. 93). Both in later stages may give the impression of a xanthomatous fibro-adenoma.

(c) Xanthoma Cells in Osteitis Fibrosa Cystica Disseminata (Fibrous Dysplasia)

Snapper and Pansel[11] and Snapper[16] in his book on bone diseases reported cases of osteitis fibrosa cystica disseminata (fibrous dysplasia) with nests of foam cells in the fibromatous tissue. The presence of localized nests of single foam cells in some areas of the fibromatous growth in this disease has been confirmed by other authors. Snapper's

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(d) *Xanthomatous Transformation of the Mesentery and Intestinal Lipodystrophy of Whipple*

Xanthomatous changes of the mesentery take place in the areolar tissue of the radix mesentery. The submucosa of the jejunum and the lymph nodes in the vicinity of the xanthomatous changes are replaced by fibrous or xanthomatous tissue. Cases of xanthomatosis of the mesentery have been reported by Pick and Pinkus[40] Verse[56] Schlagenhauser[43] Hirsch[6] Karolny and Petri[3] Seven cases were described by Hirsch[6] 28 by Verse[6] and 8 by Karolny. Most of Karolny's patients were elderly and overnourished. These facts should indicate that xanthomatous changes in the mesenterium are frequent but probably overlooked.

Verse[6] attempted to explain these changes by a blocking of the lymphatic vessels by mechanical factors. Karolny, on the other hand, considered the mechanical hypothesis advanced by Verse inadequate. He was unable experimentally to reproduce the xanthomatous changes in the mesentery by compressing or ligating the thoracic duct.

Whipple[9] described a condition in which the submucosa of the jejunum and the peritoneal and retroperitoneal lymph nodes of the mesentery contained yellow patches of xanthoma cells and hemorrhagic areas with hemosiderin. Reinhart and Wilson[4] who reported a similar case of intestinal lipodystrophy (Fig 94) attempted to relate the disease to various undetermined conditions of malabsorption of fat as reported by Blumgart[5] and Jarcho[2]. However, the latter cases are apparently different because no xanthomatous transformation of the mesentery was reported.

The clinical picture in the description of Whipple[58] as well as that of Reinhart and Wilson[4] was that of a progressive cachectic disease with diarrhea and fatty stools. On the other hand the clinical histories reported as xanthomatous transformation of the mesentery (Schlagenhauser[43] Verse[6] and Karolny) did not mention fatty stools and diarrhea but only inflammatory diseases of different etiology in different organs of the patients. At autopsy xanthomatous changes were found accidentally in the mesentery.

In the author's opinion there is little doubt but that the anatomical descriptions of Whipple[55] as well as Schlagenhauser[43] and the other authors are the same, namely xanthomatous transformation of the mesentery and lymph nodes. Apparently the extensive development of foam cells in the fat tissue of the mesentery may be the result of etiologically different occurrences, most probably of inflammation of the fat tissue.

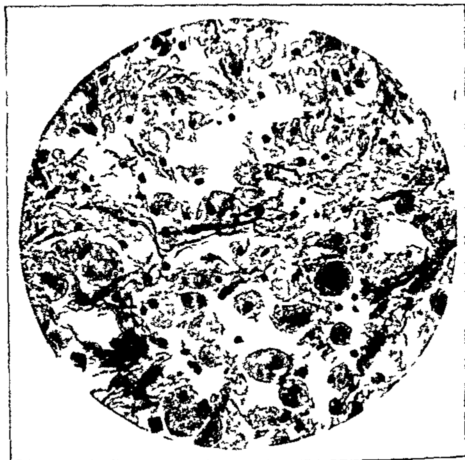


Fig 93 Inflammatory xanthoma of the breast (high power) The tumor is composed of large xanthoma cells lying in the interstices of a fibrous stroma The xanthoma cells are round when they lie free and polyhedral when they lie among the strands of a fibrous stroma (From Haagensen[17])

opinion however that fibrous dysplasia (osteitis fibrosa cystica disseminata) is related to the Schuller Christian syndrome because of these localized areas of foam cells does not seem justified The histological cellular structure of the bone lesions is entirely different in both conditions Local chronic inflammation in between the larger areas of fibromatous growth may have occasioned the development of foam cells or the foam cells may have originated from reticular and histiocytic cells remnants of the bone marrow interspersed in the fibromatous growth of fibrous dysplasia

made the following statement It is our opinion that the typical lesions of Whipple s disease as described by him were the massive accumulations of intracellular and extracellular fat in the small intestine and its draining lymph nodes with dilation (probably resultant) of lacteals and mesenteric lymphatics and that if these are considered the pathologic criteria for the disease the only cases that definitely can be included after Whipple s description at least until more is known about the pathogenesis are in chronologic order those of Jarcho Hill Korsch Glynn and Rosenheim, Reinhart and Wilson Sailer and McGann Apperly and Copley Vaux Amsterdam and Grayzel and Fitzgerald and Kinney

Rosen and Rosen believe that the accumulation of fatty material and foam cells in the jejunal mucosa in the mucosal and submucosal lymphatics are not properly considered by Thannhauser[49] as the primary focus of the disease despite the fact that Whipple in his original description called attention to this submucosal accumulation of foam cells in the small intestines This author is in complete agreement with Rosen and Rosen that the intestinal submucosal accumulation of fat and xanthoma cells together with the same changes in mesenteric lymph nodes and xanthomatous transformation of the mesentery are the characteristic histological findings of Whipple s intestinal lipodystrophy Thannhauser suggested however that xanthomatous transformation of the mesentery and lipid deposits in lymph nodes should not be considered as incidental findings at autopsy but should be related to Whipple s lipodystrophy even if the clinical features do not suggest the diagnosis of Whipple s disease This author saw histological slides with typical submucosal accumulation of foam cells in a patient whose clinical features did not suggest the correct anatomical diagnosis of Whipple s lipodystrophy For this *reason it is not surprising that xanthomatous* transformation of the mesentery usually is only diagnosed at autopsy while the clinical syndrome may be absent or at least not outstanding

Partial obstruction in the lymphatic drainage of the small intestines and malabsorption of the lipids probably due to a disturbance of the various enzymes concerned with fat splitting or fat resynthesis in the intestinal mucosa may occur together and result in the disorder described by Whipple The interference with the absorption of lipids may however be of a minor degree and consequently the characteristic clinical feature of diarrhea may be absent In such cases the clinical diagnosis will be missed and only the autopsy reveals the disorder under discussion

The history of the case reported by Rosen and Rosen[4] may be quoted as an example of Intestinal Lipodystrophy of Whipple

in the mesentery quite similar to that of the fat tissue in the breast. Therefore xanthomatous transformation of the mesentery can not be considered as a disease with distinct clinical symptoms. It must rather be regarded as a not too infrequent condition, occurring after inflam-

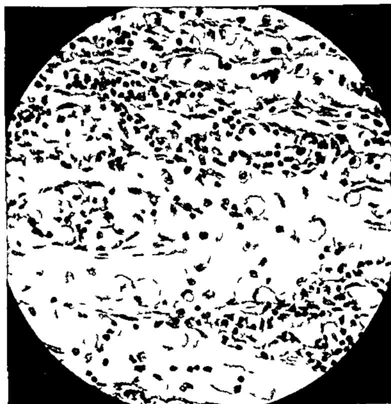


Fig. 94. Xanthomatous transformation of a mesentery. High magnification. Note large layers of foam cells in inflammatory tissue of the mesentery surrounding a lymph node. Histological slide through the courtesy of Dr. H. L. Reinhart, Columbus, Ohio; also see Am. Jour. Path., 1939, XV, 483.

mation of the fat tissue in the mesentery, in which xanthoma cells in stripes and conglomerates are revealed upon autopsy.

During the last year cases belonging to this group have been reported by Boeck[6], Sailer and McGann[4b], Pearse[37], Apperly and Copley[3c], Amsterdam and Grayzel[3b], Vaux[5], Glynn and Rosenheim[11], Fitzgerald and Kinney[1], Rosen and Rosen[4], and Chapnick[8].

M. S. Rosen and Samuel H. Rosen[4], who did an extensive study of the literature presenting a case of intestinal lipodystrophy of Whipple

spleen was felt 4 fingers breadth below the costal margin There was 1 plus pretibial edema Reflexes were hypoactive The impressions were Banti s syndrome general paresis, acute gastro enteritis

Laboratory Findings—The Wassermann and Kahn tests were 4 plus Kline test 3 plus Urine specific gravity 1 0 0 and 1 013 with albumin 0 to a trace glucose a trace to plus up to 10 white blood cells per high power field No blood count was done For chemical analyses see Table XXXII

The patient received antiluetic therapy in the form of bismuth in oil liver injections and mercupurin The diarrhea subsided somewhat On July 3 1945 abdominal paracentesis released 500 c c of straw colored fluid with 0 8 per cent protein During the last few weeks of her life increasing muddy pigmentation of the skin was noted She had periods of confusion hysteria and depression Her mental status was considered to be due to tertiary lues

On July 17 1945 the patient suddenly had copious coffee ground vomitus went into shock and appeared to aspirate much vomitus soon becoming livid All measures to relieve her were futile and she died about 4 hours after the onset of these symptoms (For autopsy see original article of Rosen and Rosen)

TABLE XXXII

Lipid Analysis of Mesenteric Lymph Node and Jejunum of Rosen and Rosen

		Mgm per 100 mgm of dried tissue	
	Normal values for Lymph nodes and spleen	Mesenteric lymph nodes	Jejunum
Total lipids		73 5	53.4
Phosphatide			
(Phosphorus == total phospholipid)	5 5–11.0	5.8	4.9
Total cholesterol	0 5– 1 2	6 1	4
Total fatty acids	8.0	64.0	41 5
Free fatty acids		12 1	3 7
Saponification number	—	166	150

Normal Values Thannhauser and Reinstein[19] Freud Grossman and Dragutsky[13]

(e) Xantholipomas

Xantholipomas are described as large lipomas containing foam cells In a case described by Adair Pack and Farrior this kind of xantholipoma degenerated into a liposarcoma (Fig 95) Proescher and Mere

Clinical Case

Case XLV — The patient, I W, was a Russian born white female 54 years old who was seen on April 10, 1945 by a private physician She complained of increasing abdominal pain weight loss of 10 lbs in 6 months, poor appetite and obstinate constipation

On April 2[illegible], 1945 the patient entered Bronx Hospital Her complaints then were weight loss of 15 lbs, weakness, and diarrhea of [illegible] weeks duration She stated that she had 4 to 5 bowel movements daily and that the stool was dark green and showed no blood Prior to the onset of diarrhea, she had been constipated for several years, taking senna without effect

On examination the patient was lying in bed, in no apparent distress Malar telangiectases were noted The blood pressure was 112/60 mm Heart and lungs were negative The abdomen was large and distended A mass later interpreted as spleen, was felt 4 fingersbreadth below the costal margin in the left side There was no peripheral edema Reflexes were normal

Laboratory Findings —The urine showed a trace of albumin Examinations of the blood on two occasions revealed the hemoglobin to be 7[illegible] and 68 per cent red blood cells, 4 61 and 4 [illegible]7 million white blood cells 14 500 with 37 per cent polymorphonuclear leucocytes 54 per cent lymphocytes 8 per cent monocytes and white blood cells 11 700 with 43 per cent polymorphonuclear leucocytes 54 per cent lymphocytes 1 Turk cell Icterus index was 7 Total cholesterol was 142 9 mgm per cent with 57 per cent esters Stool culture was negative for the typhoid dysentery group and there was no occult blood Sternal puncture revealed normal bone marrow Total proteins were 6 33 gm per cent with 3 3[illegible] gm per cent of albumin and 3 01 gm per cent of globulin Takata Ara test was negative Cephalin flocculation test was 2 plus The Wassermann test was doubtful and the Kahn test negative on one occasion but later each was reported as 4 plus Roentgenograms of the abdomen showed the spleen to be enlarged to the umbilicus and a stone of the biliary type in the gallbladder region

The patient was afebrile through her stay On April 26 a moderate amount of fluid was noted in the abdomen She was discharged on May 15 1945 with the final diagnosis of cirrhosis of the liver and lues

She entered the Montefiore Hospital on May [illegible]9 1945 She then complained of having had heart disease for 3 months, diarrhea and weight loss for [illegible] months There had been no vomiting and no tarry or bloody stools She claimed to be having eight bowel movements a day There was also a dubious history of numerous bouts of congestive circulatory insufficiency

Examination revealed a noisy female with no dyspnea or othopnea Temperature 98 F pulse 90 blood pressure 108/6 mm Pupils were contracted and reacted poorly to light There was an apical systolic murmur and an accentuated second aortic sound The abdomen was distended The

2 Xanthoma Cells in Tumors

a Nevo xanthoma endothelioma (Juvenile Xanthoma)

In the discussion on juvenile (infantile) xanthoma (nevo xanthoendothelioma) and its relation to and variation from the skin lesions of eosinophilic xanthomatous granuloma the clinical features and the histology of juvenile xanthoma were pointed out and a typical case history of juvenile xanthoma presented It was also suggested that the histological designation nevo xantho endothelioma as a misnomer should be abandoned since true nevus cells are not found in the lesion The early lesion consists of proliferating endothelial cells of capillaries proliferation of reticulum cells which develop in a later phase into foam cells and proliferation of fibroblasts Giant cells of the Touton type are present The lesion occurring in the first year of life may disappear in later life completely If other organs except the skin are involved as in Lamb and Lain's case[30] the diagnosis should be revised and eosinophilic xanthomatous granuloma (Schuller-Christian syndrome) is suggested for the diagnosis Cases of juvenile xanthoma were described first by Adamson in 1905 but defined by McDonaugh[3] in 1909 Other cases are published by Wise[8] Jacobi and Grund[6] and Senear and Caro[44] The cholesterol phospholipid and neutral fat in the serum of such infants are normal The children are healthy and develop normally

b Xanthomatous Polycystic Lymphangiomas

Smith[46] Pick[46] and Kirch reported polycystic xanthomatous lymphangiomas of the tongue and labium majus pudenti as well as of the parotid gland The xanthoma cells of these tumors originate from the endothelial cells They contain iron hemosiderin and are sometimes erroneously called pigmented xanthoma tumors The xanthomatous hemangiomas also belong to this group

c Single Xanthomatous Giant Cell Tumors

These tumors are often confused with the tendon xanthoma which are a part of the tendon and a feature of essential hypercholesteremic familial xanthomatosis and occur together with xanthoma planum et tuberosum of the skin These giant cell tumors are single encapsulated lobulated tumors arising from the tendon and not part of a systemic disease They have been described by Chassagnac[3], Spencer Wells[43] Billroth[3]

dith[11] described cases of multiple myxocholestolipoma, two intra abdominally and one in the retroperitoneal space Sometimes, the xantholipoma may be located in the joint, where it may develop after trauma and bleeding This type of xantholipomas should not be confused with

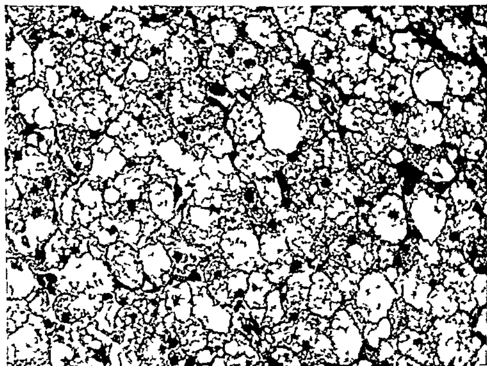


Fig 95 Xantholipoma with typical foam cells The bulk of the tumor is composed of large spherical cells with scant intracellular substances The cytoplasm is foam like coarsely granular and contains numerous vacuoles Mucinous degeneration is observed in some regions The histological diagnosis is benign xantholipoma or myxo liposarcoma (Reproduced from Adair F E., Pack G T and Farrior J H[2])

tendon xanthoma of hypercholesteremic familial xanthomatosis, which also may originate in the joint especially in the ligamentum cruciatum In the first type the xantholipomas arise in the synovial membrane or in fat tissue In the other type the xanthoma arise from a fascia or tendon simultaneously with other features of hypercholesteremic familial xanthomatoses Galloway Broders and Ghormley[11] recently published an extensive review of this subject



Fig 96 Lipoid Proteinosis (Urbach) Note the scar like nodules on the face The color is brownish (From Urbach E., Epstein E and Lorenz K [33])

the majority of the lesions on the mucous membranes are of the same color as the surrounding mucosa or are purplish and only a few of the larger lesions are suggestive clinically of xanthoma The cutaneous lesions in lipoid proteinosis resemble those of neurodermatitis or of an epithelial nevoid disturbance more than those of xanthoma and as a rule they lack any yellowish hue' There are no xanthoma cells present but hyper keratosis and irregular acanthosis are found The capillaries of the sub cutaneous tissue are surrounded by a mantle of lipids The hematoxylin

and Czerny[10] Their histological structure resembles that of a sarcoma of the epulis type They contain spindle or round cells, giant cells and hemosiderin These tumors have been called "xantho-sarcoma' by the English and "xanthomatous fibro-sarcoma" by the Germans However, the malignant nature of these tumors is doubtful They seem to be in many instances benign neoplasms of connective tissue, where the xanthoma cells are a more or less incidental finding in a fibroma or fibrosarcoma

d Epithelial Tumors with Xanthoma Cells

Corten[9] described a tumor, the size of a fist, of the subcutaneous tissue The occurrence of pale bodies surrounded by foam cells suggested its epithelial derivation These tumors were assumed to have arisen from a misplaced anlage of a sebaceous gland Kinoshita[3] described xanthoma cells in a prostatic carcinoma Petri[38] found that the cells in an adenocarcinoma of the stomach with its metastasis in the liver assumed the appearance of typical foam cells However, after analyzing Petri s report the author believes that the condition described belongs to the group of eosinophilic xanthomatous granuloma in which the lymph nodes liver, lining of the stomach and capsule of the spleen are involved, while the adenocarcinoma of the stomach is an independent feature Dubs[11] reported the development of xanthoma cells in the connective tissue of two cases of adenocarcinoma of the uterus Kneringer and Priesel[9] found foamy structures in a thymoma Ewing[1] described foam cells with lipid materials in a hypernephroma

It is evident that the occurrence of xanthoma cells in any kind of tumor has nothing to do with the origin of the tumor In any kind of neoplastic tissue cells of reticular origin in rare instances may develop into foam cells

C SUPPLEMENT

1 Lipoid Proteinosis

Urbach and Wiethe described as 'lipoidosis cutis et mucosae yellow hyperkeratotic lesions of the skin (Fig 96) and mucous membrane (Fig 97) This observation was confirmed by several authors especially Montgomery and Havens[34], who examined these lesions histologically and chemically They state In lipoid proteinosis, on the other hand

This man was admitted to the Massachusetts General Hospital in 1938 with a diagnosis of epidermolysis bullosa. A biopsy specimen was not confirmative. In addition to the cutaneous disturbances this man had the following symptoms. He had been hoarse ever since he could remember. During the past ten years he had occasionally experienced "mirages," which sounded like visual hallucinations from the patient's description. For the past five years he has had "fainting spells" with increasing frequency. These seizures are epileptiform in type. Treatment in the neurological clinic by means of bromides, barbiturates and dilantin sodium failed to control the attacks. The family history was negative except that the patient thought one of his antecedents had diabetes.

On *physical examination* almost all of this patient's skin revealed an ivory or yellowish color of varying degrees as well as a severe scarring most marked on the face, the extensor aspects of the extremities and the buttocks. The scars, which varied from 0.5 cm. to 1.5 cm. in size, were pale, atrophic and occasionally appeared varioliform. At the time of the last examination there were no infections present. On some occasions there had been numerous crusted ulcers of the eczematous type on the face, intergluteal or scrotal regions. Multitudes of tiny miliary papules of yellowish white color were seen on the face and neck and were particularly noteworthy along the margins of the eyelids. These lesions, uniform in size, measured about 1 mm. in diameter. The knees, elbows and buttocks revealed irregular areas of thickening suggesting hypertrophy of the skin rather than a lichenoid thickening. This change was most pronounced in the internatal cleft between the scars. The miliary lesions were present also in the oral and faucial mucous membranes. Several of the patient's teeth were missing; some of these had been knocked out when he fell during a seizure. However, it was the opinion of the dental department that this man might also have some degree of congenital anodontia (possibly lesions of the sockets of the teeth as in Schuller-Christian syndrome—Author). The maxillary canine teeth were unusually pointed in structure. There were some enamel deformities in the nature of notably hard and thick formations. Laryngoscopic examination revealed an irregular thickening of the vocal cords.

Laboratory findings were as follows. The Hinton and Wassermann tests of the blood were repeatedly negative. Blood counts and urine examinations were always normal. The report on a *biopsy specimen* taken in 1938 stated that there was "no diagnostic abnormality; elastic tissue normal; the central arteriole of each papilla shows a uniform cord of fat forming a sheath about the blood vessel." A second piece of tissue removed in 1944 revealed a moderate hyperkatosis and moderate to marked atrophy of the epidermis. The corium was twice to three times its normal width. Phloxine methylene blue stains revealed that the upper third to upper half of the corium was occupied by a nearly homogeneous, slightly basophilic material. Scattered

and eosin stain show a peculiar type of homogenization of the connective tissue suggesting a hyalin degeneration Thannhauser and Magendantz[19] believe that lipoid proteinosis is not an independent clinical picture but the fibrotic phase of xanthoma disseminatum (eosinophilic xanthomatous granuloma of the skin), resulting in scar tissue producing so-called lipoid proteinosis These authors came to this conclusion because the same yellow-orange deposits were observed under the surface of the tongue (Fig 97) and other mucous membranes together with xanthoma disseminata in the case described by Turner, Davidson and White[0] Montgomery and Havens[31] patient had papulo-squamous slightly infiltrated plaques of a brownish hue on elbows and knees pharyngeal walls and under the tongue Montgomery and Osterberg[31a] found that lecithin is increased in the tissue and blood

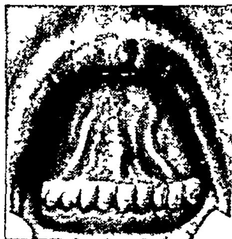


Fig 97 Lipoid Proteinosis (Urbach) Note the fibrous infiltrated stripes under the tongue The stripes are of a yellowish white color (From Urbach E)

Clinical Case

Case XLVI—J S a 30 year old white laborer was described by Dr G M Crawford and Dr I M Thurmon as a case of generalized lipoid proteinosis before the New England Dermatological Society on October 18 1944[9] The patient first had infections on his face scalp trunk and extremities when he was about five years old Lesions appearing from time to time on various portions of those areas often required months to heal They frequently came in crops once or several times a year and resulted in pronounced scar formation

The patient developed mirages and seizures at the age of twenty It is highly suggestive that these epileptiform attacks were caused by lesions of the brain similar to those observed in the skin The epileptic syndrome caused by eosinophilic xanthomatous lesions of the brain as described in cases of Schuller Christian syndrome Case XLI and XLII which occurred together with skin lesions of the same disorder favor the opinion of the author that lipid proteinosis is the late fibrotic phase of eosinophilic xanthomatous granuloma (Schuller Christian syndrome)

. Necrobiosis Lipoidica Diabeticorum

Oppenheim[6] (19 9) described as dermatitis atrophicans maculosa lipoides diabetica skin lesions which were designated later by Urbach[4] as necrobiosis lipoidica seu diabetica These lesions begin with an intensely red hard lentil sized peripherally growing raised papule Later the center sinks in assumes a scleroderma like consistency and becomes sulphur yellow The periphery has a small zone of violet red discoloration (Fig 9[8]) The yellow part is flecked with dark spots and traversed by numerous telangiectases Occasionally there is some scaling There is no resemblance to xanthelasma There should be no reason at all for confusing the nevous like epithelial disturbance with skin xanthoma especially since the atrophy of the center is the main feature and marginal yellowish brown pigmentation secondary There is in most cases extensive necrosis of the upper layers of the cutis and large number of droplets staining with Sudan III in the necrotic zone Although the droplets contain extracellular fat like substances which infiltrate the necrotic mass in the subcutaneous tissue they do not contain cholesterol This condition is observed mostly in patients with diabetes Goldsmith[3] and Klaber[2] reported cases where the patient was not diabetic, yet had high blood sugar

Urbach[4] suggested that the primary damage is in the walls of the blood vessels. The lipoids seem to be imbibed from the blood secondarily "Necrobiosis lipoidica diabeticorum has nothing in common clinically with the eruptive form of xanthoma in diabete The eruptive form which appears and disappears is due to hyperlipemia In necrobiosis lipoidica diabeticorum hyperlipemia is not a prerequisite for the disturbance The clinical resemblance to erythema induratum (Darier Roussy) or dermatitis atrophicans often may be confusing These conditions are even similar histologically only the yellow discoloration of the skin and fat staining reveal extra-cellular lipids in great amounts

small foci consisting of lymphocytes monocytes and fibroblasts were present The walls of the capillaries were considerably thickened due to infiltrations with the same homogeneous material Fat stains showed diffuse infiltration of the upper corium with small fat droplets The largest amount of fatty infiltration was seen around some of the capillaries The deposit of fat was extracellular No foam cells were observed Chemical analysis of skin is shown in Table XXXIII The histological picture thus was consistent with lipid proteinosis Examination of the cerebrospinal fluid was normal A roentgenogram of the skull showed calcification of the tentorium bones of the extremities were normal An electroencephalogram was found to be abnormal and suggested tumor formation The cholesterol of the blood in 1938 was 151 mgm per cent and in 1944 was 235 mgm per cent Additional blood chemistry findings in 1944 were as follows non-protein nitrogen 20 mgm per cent protein 6 8 gm per cent, chloride 106 mgm per cent and sugar 8 mgm per cent, serum analyses are shown in Table XXXIV

TABLE XXXIII

Tissue Analysis (J Bernotti and S J Thannhauser)

Weight of skin specimen without subcutaneous fat	0 336 gm	
Phospholipid phosphorus per 100 gm tissue	0 0 4 gm	
(This phospholipid phosphorus was entirely saponifiable which indicated that the complete phospholipid phosphorus was derived from lecithin and cephalin but not from sphingomyelin)		
		Normal
Lecithin and cephalin	0 600 gm %	0 1-0 5
Neutral fat	0 26	
Total cholesterol	0 550	0 1-0 34
Free cholesterol	Only traces	Traces

TABLE XXXIV

Serum Analysis

Total cholesterol	[illegible] mgm %
Free cholesterol	74
Cholesterol present as esters	155 "

Comment

It is of great interest that this patient had epileptic seizures of the diencephalic type with visual hallucinations of the same type observed in adults (see cases XLI and XLII) who had bone and skin manifestations of eosinophilic xanthomatous granuloma (Schuller Christian syndrome)

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FIG 98 Necrobiosis Lipoidica Diabeticorum The areas exhibit bluish pink color In the center of the lesion are distinct small yellowish-ochre colored patches (From Urbach F 54)

which are not present in erythema induratum No effective therapy is known

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replaced by large pale cells in a case of splenohepatomegaly He attributed this condition to a primary epithelioma of the spleen

It was not until thirteen years later that Collier[7] in England and Picou and Ramond[109] in France described the next cases of this disease These investigators also regarded the condition as neoplastic Bovaird[17] (1900) reporting cases in this country called attention to the appearance of the large cells in the liver as well as in the spleen and lymph nodes He had already commented upon the familial character of the disease Disagreeing with the view that it was a neoplastic process he described the condition as hyperplasia of the spleen, liver and lymph nodes produced by the irritating effect of some unknown toxin Brill Mandlebaum and Libman[9] (1905) were the first to point out that Gaucher's disease not only involves the spleen and liver but also different parts of the skeleton simultaneously Schlagenhaufer[1] (1906) who reported cases of the disease in Germany referred to the affection as a systemic disease of the lymph hemopoietic system He suggested that the tuberculosis which frequently is found concurrently might be of etiological importance Marchand[3] (1907) who made a histological study of the diseased organs was the first to suggest that the process was neither neoplastic nor a simple hyperplasia According to this author the enlargement of the cells results from a deposit of some foreign substance Brill and Mandlebaum[19] (1913) proposed the name Gaucher's disease to avoid the misleading term primary idiopathic splenomegaly Oberling and Woringer[96] (19 7) described a special form of Gaucher's disease which occurs in infancy in siblings The brain is involved also in these infantile cases and the infants usually die within the first two years

Analogous to Pick's conception that xanthomatosis is a storage disease where the cholesterol is transported by the blood stream and stored in the cells it was believed that Gaucher's disease also was a storage disease in which the kerasin is supplied and stored in a similar manner Epstein and Lorenz[4] in association with Lieb[73 74] were the first to determine that the substance deposited in the cells is a cerebroside kerasin This finding has since been confirmed by Cushing and Stout[29] Pick[107] Bloom and Kern[1] as well as other investigators Thannhauser Benotti and Reinstein[13] demonstrated that kerasin as well as the other cerebrosides are not normal constituents of the blood serum On the basis of these findings they showed also that these cerebrosides were not present in the serum in Gaucher's disease Thannhauser and coworkers abandoned the conception of Gaucher's disease as a storage disease produced by an increased supply of cerebrosides from the blood stream

PART IV

IV GAUCHER'S DISEASE (RETICULAR AND HISTIOCYTIC CEREBROSIDOSIS)

Definition

Synonyms.—Primary idiopathic splenomegaly, Gaucher's large celled splenomegaly, lipoid cell splenohepatomegaly, Gaucher's type, cerebroside lipoidosis.

Definition.—Gaucher's disease is a rare familial constitutional disorder of the cellular metabolism in the lymph hemopoietic organs. It is characterized by an accumulation and retention of cerebrosides in the reticular cells and histiocytes of these organs. The resulting hyperplasia of reticulum cells and histiocytes leads to an overgrowth and enlargement of the spleen, bone marrow, liver and lymph nodes which are the organs involved in the disease. The deposition of hemosiderin iron in the various organs is a secondary process, which may occur in reticular and histiocytic cerebrosidosis.

The following clinical manifestations are found in Gaucher's disease, (1) enlargement of the spleen, (2) skeletal changes caused by destructive infiltration of the cerebrosidic reticulosis of the bone marrow, (3) enlargement of the liver and the lymph nodes, (4) pigmentation of the skin which is patchy and similar to cloasma in pregnancy and has nothing to do with exposure to light, (5) cuneiform thickenings of the conjunctiva as well as brownish discoloration of the conjunctiva near the cornea, (6) hemorrhagic tendencies due to thrombocytopenia. Changes in the white cells of the blood are not characteristic, but leukopenia is frequent. Microcytic anemia and general emaciation are found in advanced stages of the disease. Spontaneous pain in some places of the bony skeleton, especially the femur, accompanied by fever may be an early symptom in the first stages of the disease.

Historical Note

Phillip Charles E. Gaucher in 1882 was the first to describe the disease which today bears his name. In a paper "De l'epithelioma primitif de la rate" which was submitted as a thesis to the faculty of medicine at Paris, Gaucher reported that he found the splenic pulp entirely

reported by Brill Mandlebaum and Libman[1] the spleen weighed 8,100 grams and measured 45 × 25 × 13 cm

The general contour of the spleen is preserved The surface, as a rule is smooth but thickening of the capsule and perisplenitis may be seen in cases of long duration Occasionally the surface is irregularly elevated as a result of hemorrhage It may be depressed also because of healed infarcts The color is dark purple or brownish red The consistency usually is firm and on section the cut surface feels smooth It has however a mottled coloration as a result of scattered semi translucent areas about one millimeter in diameter In more advanced stages these translucent areas fuse to form a grayish white network The malpighian corpuscles become widely separated and obscure Hemorrhagic and cavernous areas are found frequently Large anemic infarcts may occur near the surface The arteries and veins usually are dilated and thin walled The hilus veins may be thickened in a late stage of the disease A cluster of enlarged lymph nodes usually is found at the hilus and along the splenic vein

Although the liver is generally increased in size the enlargement is not nearly so great proportionately as that of the spleen There are however exceptions in which it does not appreciably exceed a normal weight Its consistency is firm The surface is smooth and glistening and the color a light yellowish brown In later stages of the disease the capsule is thickened in places due to areas of perihepatitis The surface becomes grayish brown and on section brownish pink or red with grayish ramifying streaks which seem to have no definite relation to the lobular markings The connective tissue is increased giving in the advanced stage a cirrhosis like appearance which is not as regular as that in hypertrophic cirrhosis At times hemorrhagic points are noted The portal and hepatic veins appear normal

The superficial lymph nodes may be enlarged However those in the thorax and abdomen are always increased in size They measure from one half to two centimeters in diameter and usually are soft The mesenteric and retroperitoneal nodes are relatively larger than the other abdominal lymph nodes In children the tracheobronchial and esophageal nodes are increased in size occasionally the axillary and inguinal lymph nodes also are enlarged The color is dark red yellowish red or brownish black with grayish white small dots even in the nodes which are not especially enlarged (Rowland)[119]

The involvement of the skeletal system is as characteristic in Gaucher s disease as the involvement of the spleen It is one of the main

These investigators attempted to demonstrate that reticular and histiocytic cerebrosidosis is a disease in which the intracellular metabolism in some of the reticular cells and histiocytes is disturbed by an unbalance of enzymes concerned with the synthesis and disintegration of sphingomyelin and cerebrosides within the cell

Aghion as well as Halliday and coworkers[4b] found that cerebrosides accumulated in the organs of patients with Gaucher's disease are not galactosidocerebrosides as was formerly demonstrated by Epstein and Lorenz[4] in association with Lieb[3, 4], but consist of glucosidocerebrosides Klenk[68a, 68b], Danielson Hall and Everett as well as Polonski[100] confirmed the presence of glucosidocerebrosides by analysis of spleens in Gaucher's disease Of three different spleens in cases of Gaucher's disease examined in our laboratory (Ottenstein, Schmidt and Thannhauser[9]) two spleens contained glucosidocerebrosides only (8 3 mgm per cent and 11 3 mgm per cent respectively) while one spleen had 7 mgm per cent glucosidocerebrosides as well as 8 6 mgm per cent galactosidocerebrosides These analyses demonstrated that glucosidocerebrosides are found mainly in adult Gaucher's disease although galactosidocerebrosides occur simultaneously The organs of two siblings with the infantile and generalized form of Gaucher's disease were analyzed by Ottenstein Schmidt and Thannhauser[9] In the organs of one infant only the galactoside variety of cerebrosides was found while those of the other infant showed both kinds of cerebrosides It now seems evident that the cerebrosides accumulated in the reticulum cells and histiocytes in Gaucher's disease are more often of the glucoside variety, a physiologically unusual kind of cerebroside However, the galactoside variety the physiological form found in brain and to a minor degree in normal organs may also be accumulated together with the glucosidocerebrosides in the organs involved in Gaucher's disease

Morbid Anatomy and Histology

The most striking features found at autopsy are massive hypertrophy of the spleen enlargement of the liver and lymph nodes and gross skeletal involvement The spleen is always enlarged and occasionally of enormous size Its size and weight depend on the duration of the disease and the age of the patient The average weight found in 25 adult cases was 2,800 grams In 13 children the average weight was 780 grams In a case

reported by Brill, Mandlebaum and Libman[11] the spleen weighed 8 100 grams and measured 45 × 25 × 13 cm

The general contour of the spleen is preserved The surface as a rule, is smooth but thickening of the capsule and perisplenitis may be seen in cases of long duration *Occasionally the surface is irregularly elevated* as a result of hemorrhage It may be depressed also because of *healed infarcts The color is dark purple or brownish red* The consistency usually is firm and on section the cut surface feels smooth It has however, a mottled coloration as a result of scattered semi translucent areas about one millimeter in diameter In more advanced stages these translucent areas fuse to form a grayish white network The malpighian corpuscles become widely separated and obscure Hemorrhagic and cavernous areas are found frequently Large anemic infarcts may occur near the surface The arteries and veins usually are dilated and thin walled The hilus veins may be thickened in a late stage of the disease *A cluster of enlarged lymph nodes usually is found at the* hilus and along the splenic vein

Although the liver is generally increased in size the enlargement is not nearly so great proportionately as that of the spleen There are however exceptions in which it does not appreciably exceed a normal weight Its consistency is firm The surface is smooth and glistening and the color a light yellowish brown In later stages of the disease the capsule is thickened in places due to areas of perihepatitis The surface becomes grayish brown and on section brownish pink or red with grayish ramifying streaks which seem to have no definite relation to the lobular markings The connective tissue is increased giving in the advanced stage a cirrhosis *like appearance which is not as regular as that* in hypertrophic cirrhosis At times hemorrhagic points are noted The portal and hepatic veins appear normal

The superficial lymph nodes may be enlarged However those in the thorax and abdomen are always increased in size They measure from one half to two centimeters in diameter and usually are soft The mesenteric and retroperitoneal nodes are relatively larger than the other abdominal lymph nodes In children the tracheobronchial and esophageal nodes are increased in size occasionally the axillary and inguinal lymph *nodes also are enlarged* The color is *dark red yellowish red or brownish black* with grayish white small dots even in the nodes which are not especially enlarged (Rowland)[119]

The involvement of the skeletal system is as characteristic in Gaucher s disease as the involvement of the spleen It is one of the main

features of the disease Gross anatomical changes may be found in all bones especially in the femur, sternum and vertebræ (Fig 99) The bone marrow is soft in consistency, red in color, with small white or yellow masses scattered irregularly throughout These masses may be as large as a chestnut or as small as the head of a pin There may be areas of necrosis of the bone marrow with definite discoloration and even the appearance of pus may be simulated Fasciculated scar tissue may be found in the neighborhood of these soft masses of the bone

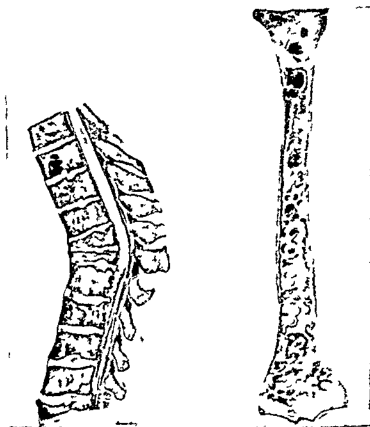


Fig 99 Gaucher's disease Section of a femur and spinal column Note the destruction of two vertebræ and the thinning of the cortex of the bone and the femur (From Pick L)

marrow However, even in this scar tissue Gaucher cells are found by histological examination

Histologically (Figs 100 and 101) the Gaucher cells in the bone marrow are similar to the Gaucher cells in other organs but Pick

describes definite Gaucher cells with spindle form Piel's classical description of the histological changes in the bone marrow is the best and the most complete The osseous substance of the bone is involved because the proliferation of Gaucher cells decalcifies and rarefies the osseous structure *Therefore the appearance of the bones is changed* *The most* characteristic feature in this respect is bulging of the distal third of the femur The waistline of this part of the femur has completely disappeared (see Fig 99) The x ray appearance of the femur is like that of an



Fig 100 Gaucher's disease Bone marrow (low magnification) Note that the bone marrow is filled out with Gaucher cells Through the courtesy of Dr Sidney Farber Pathological Department of the Children's Hospital Boston

Erlenmeyer flask (Fig 108) The flaring of the long skeletal bones is not restricted to the femur but may be found also in the tibia and humerus The rarefication of the osseous skeleton by Gaucher cells may lead to a complete destruction of one or two vertebrae in the spine as well as to a true gibbous formation (Fig 99) Spontaneous fractures of the bone are observed in severe cases of Gaucher's disease (see Fig 110)

The periosteum is not involved in this process The joints especially those of the knee and hip frequently are affected secondarily The

destruction of the osseous skeleton by the Gaucher masses produces the deformities of the bones, consequently leading to secondary joint diseases with and without effusion and deformities

Bony changes of the jaw, both in the mandible and the maxillae have been described in two cases Gaucher cells were found also as an exception in the periosteum The following findings have been reported generalized porosity pseudocystic areas of radiolucence in the man dibular region and the presence of osteolytic lesions in the premolar areas

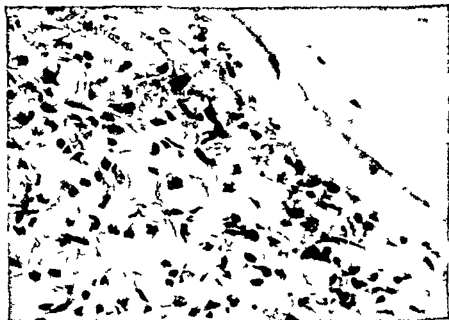


Fig 101 Gaucher's disease Bone marrow (high magnification) Note that the bone marrow is filled out with Gaucher cells Through the courtesy of Dr Sidney Farber Pathological Department of the Children's Hospital Boston

Clinical signs of otosclerosis were found in addition to the involvement of the spleen and liver in a fifty-one year old patient with Gaucher's disease The necropsy findings revealed Gaucher cells in the marrow spaces of the os petrosum E Redslob and L Gery[115] in an important paper reported remarkable changes of the eye in the choroidea of a twenty-five year old patient The Gaucher cells which were located in the cellular tissue were mixed with other cellular elements, such as lymphocytes fibrocytes and chromatofores

Histology On microscopic examination the pathognomonic feature of Gaucher's disease is the presence of a unique large pale cell the *Gaucher cell*, in the spleen liver lymph nodes and bone marrow The grayish white translucent areas observed in these organs are colonies of such cells Because of their great number they may be regarded as the *immediate cause of the enlargement of the organs*

In contrast to eosinophilic xanthomatous granuloma (essential *xanthomatosis of the normocholesteremic type lipid granuloma*) the cerebroside loaded Gaucher cell does not develop together with a granulomatous tissue *There is hardly any cellular reaction around the Gaucher cell* A few small and large lymphocytes and plasma cells may be found *In the course of the disease the Gaucher cells do not deteriorate or* soften Their replacement by fibrous tissue is slow and demonstrable *only in the organs of older persons*

In the spleen the picture is unique and characteristic The pulp is *nearly or entirely replaced by irregularly shaped alveolar spaces con*taining Gaucher cells (Figs 10. and 103) Many of these spaces are lined by *a single layer of such cells while others are completely filled* with them This structure may give the impression of a malignant *neoplasm but there is no evidence of a destructive infiltrative process* A large number of blood corpuscles may be present and in cases of long *standing areas of hemorrhage as well as of fibrosis are common*

In later stages the hemorrhagic areas may be the seat of central *necrosis and sometimes even calcium deposits appear Brown or brown*ish yellow pigment granules which give a positive iron reaction are *found in the trabeculae in the sinus walls and to a lesser degree in the* large cells themselves

The *microscopic findings in the liver of adult cases reveal a marked* increase in interlobular connective tissue (Teilum[131]) Large numbers *of Gaucher cells are found in the center of the lobules and surrounding* the efferent veins They sometimes appear also in the lumen of the portal vein The *Kupffer cells usually appear normal The pigment in* the liver is situated in or near the walls of the large vessels and in Glis*son's capsule*

A condition entirely similar to that observed in the spleen exists *in the lymph nodes The white areas are found to be colonies of large* cells The capsule and trabeculae are thickened in the late stage of the disease and here the close *relation of the Gaucher cells to the reticulum* is especially noticeable Pigment granules giving iron reactions sometimes occur

Gaucher cells are found in all parts of the bone marrow. They appear in large compact masses or in smaller groups. Isolated cells may however be seen also. The cells are usually not so large as those found in the other organs and are often spindle shaped or elongated as if com-



Fig. 102. Gaucher's disease. Large stripes of Gaucher cells in liver. *Through the courtesy of Dr. Sidney Farber, Pathological Department of the Children's Hospital, Boston.*

pressed. A close relation to the reticulum is observed. In the late stage of the disease pigment granules are occasionally found in the region of the large vessels although this is not so pronounced as in the spleen and lymph nodes. Sclerosis, hemorrhage and necrosis appear in the later stages.

In adults the Gaucher cells are not found in the lungs kidneys suprarenals ovaries pituitary thymus or superficial lymph nodes These organs are however, involved in infantile Gaucher s and Niemann Pick s disease

The lung may be involved in the acute infantile form of Gaucher s disease In adults however the involvement of the lung must be considered as a very exceptional occurrence Three such cases have been described Merklen Waitz and Warter[8] reported the first two cases one of a fifty one year old man and the other of a twenty four year old man *In the first case the Gaucher cells were found only in the spu*

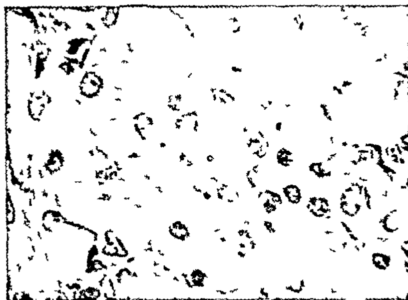


Fig 103 Gaucher cells in spleen (high magnification) Note the Gaucher cells with *several nuclei Through the courtesy of Dr Sidney Farber Pathological Department of* the Children s Hospital Boston

tum A complete necropsy which was performed in the second case revealed Gaucher cells in the liver spleen lymph nodes bone marrow *meninges as well as the lungs the brain was not involved There was no* chemical examination with special stain in either case Proof is there fore lacking that the lipid substance in the so called Gaucher cells in the lungs was really a cerebroside The same objection may be made concerning the third case (Myers[33])

The clinical picture in these three cases, however, harmonizes perfectly with that found in Gaucher's disease. Despite the fact that there was no chemical analysis, the epithelium of the lung should be considered as being involved. Since the diseases, reticular cholesterosis as well as reticular sphingomyelinosis and cerebrosidosis, are regarded as systemic diseases of the histiocytes and reticular cells, theoretically it should be possible for these cells regardless of where they are present in the organism, to be affected by deviation in their lipid metabolism. However, in lipid diseases, if there is lung involvement, the diagnosis of cholesterosis or of sphingomyelinosis should be considered before the diagnosis of cerebrosidosis (Gaucher's disease) is made.

One case was published in which there was granuloma with involvement of the kidneys. However, in this case the kidney as a whole was not affected. The authors (Horsley, Baker and Apperly[61]) reported that microexamination revealed "in one small section a space filled with cells indistinguishable from Gaucher cells". The photomicrograph showed that this area was in the interstitial tissue and not in the tubular epithelium of the kidney. These findings are not sufficient to prove that the kidney may be involved in Gaucher's disease.

Meyer[53,81] described two cases of infants with neurological symptoms. The author believes that this disease was Niemann-Pick's rather than Gaucher's disease, according to the age of the patients as well as the clinical symptoms, especially the progressive cachexia. The acute infantile form of Gaucher's disease is characterized by cerebral symptoms, so-called pseudo-bulbar syndrome with stiffness of the neck and hypertonicity of the extremities. In such cases characteristic histological changes of the brain were demonstrated[63,96,118a].

In adults there is only one case described with extrapyramidal neurological signs as well as with pigmentation and atrophy of the adrenals. This case, which also exhibited signs of Raynaud's disease, was reported by van Bogaert and Froehlich[15]. According to the clinical symptoms this was a case of Gaucher's disease. There was, however, no chemical analysis of the tissue. Only the chemical findings in the serum for cholesterol and phosphatides were published. Since phosphatides are not increased in the blood in either Gaucher's or Niemann-Pick's disease, tissue analysis and special tissue staining are diagnostically of tantamount importance and are required for diagnosis.

G. Teilum[131] in an autopsy study of a 50 year old woman with Gaucher's disease reported changes in the hypothalamus and hypophysis. Conglomerates of cells which showed the characteristic features of

Gaucher's cells were present in these areas Teilum suggests that the Gaucher cells in the brain of this case were derived from mikroglia cells He believes that the mikroglia cells of the parietal lobe of the hypophysis and of the hypothalamus may be involved in different types of diseases of the reticulo-endothelial system The involvement of these *areas in the brain in a case of Gaucher's disease is an additional feature* favoring such a theory

Pigmentation of the muscle fibers of the intestine hemorrhagic areas and pigmentation of the thigh muscles and of the uterus have been reported These conditions are due to absorbed hemorrhages Hemosiderin iron may be deposited in almost all the organs as a result of increased blood destruction In this disease the skin pigmentation is not the result of a hemosiderin deposition in the skin The normal skin pigment melanin however which is not a derivative of the iron-containing blood *pigment but a product formed by the oxidation of certain amino acids* is increased in some cases of Gaucher's disease

Local or disseminated foci of tuberculosis have been seen in several cases of Gaucher's disease These lesions which always are superimposed have no bearing on the pathological process underlying the disease

Gaucher Cells Origin and Nature

The Gaucher cell (Figs 101 to 103) is a large pale round oval or polygonal cell It is usually very large varying in size from twenty to *forty or more microns in diameter It has abundant cytoplasm crossed* by a delicate network of parallel wavy lines which give it an appearance of opaque tissue paper It contains one or more round or oval nuclei which are relatively small These have a finely granular chromatin structure and a slightly oxyphilic nucleolus The nuclei which are usually *eccentric are located near the periphery of the cell Sometimes there are* ten to twelve nuclei In such cases the cell becomes very large reaching seventy to eighty microns in diameter There are many of these giant cells which seem to be a coalescence of several cells syncytium rather than a nuclear proliferation These have been mistaken for megalokaryocytes

The protoplasm in a fresh state is homogeneous and opaque After fixation and staining with certain dyes especially Mallory's aniline blue connective tissue stain the details of the cellular structure are apparent The delicate network of wavy lines stains dark blue accentuating a

wrinkled appearance so characteristic that it is not found in any other affection The cytoplasm between these spider web wrinkles assumes a pale blue tint With the Turnbull blue method the cytoplasm may give a mildly positive iron reaction These cells do not react positively to any of the histochemical lipid staining methods After mordanting with potassium bichromate they stain a very pale yellow with Sudan III or blue with Nile blue Anisotropic bodies are seen rarely in the cells or tissues Gaucher cells are not stained with Sudan III A modification of Sudan III staining after extraction of fat from the tissue has recently been described as a specific for Gaucher cells by Franco and Wolman[116] According to Epstein[40] and Risel[118] blue staining of the Gaucher cells with Mallory stain is characteristic Smith Dietrich stains show staining of sphingomyelin but not of cerebrosides if correctly executed

The histogenesis of these cells has caused considerable controversy Some authors have described their origin from endothelium others from reticulum and quite a few claim both sources Their close relation to the reticulum and frequent inclusion in connective tissue indicate their mesenchymal origin Most investigators now agree with Piel that Gaucher cells arise from the reticulum in the spleen lymph nodes and bone marrow, from the adventitial and peri adventitial cells of the small arterioles of the splenic pulp and lymph nodes and in the liver from the histiocytes of Glisson's capsule as well as the adventitial and peri adventitial connective tissue of smaller vessels and the central lobular veins (Rowland)[119]

In the *infantile form of Gaucher's disease* where the disease is very acute and fulminating, the organs involved should be beyond the reticular endothelial system Risel[118] found Gaucher cells in the thyroid Reber[111] and Kraus[7] in the thymus and Oberling and Woring[96] in the lungs and brain In Hamperl's[4] case where Gaucher cells were found in the thymus and the villi of the small intestine as well as in the lungs, the tissue analysis later showed that the phosphatides but not the cerebrosides were increased

Chemical analysis of the organs of infantile Gaucher's disease were not carried out For this reason a considerable number of those in the earlier literature may have been Niemann Piel's rather than infantile Gaucher's disease Aballi and Kato published the first case of infantile Gaucher's disease with organ analysis of liver and spleen Robb Smith and coworkers[118] clinically and histologically studied two siblings with infantile Gaucher's disease whose organ analysis was carried out by Ottenstein, Schmidt and Thannhauser (see Table XL and XLI)

Although it is theoretically possible that other organs besides spleen liver lymph nodes and bone marrow may be involved also in adult cases of Gaucher's disease observations of such an occurrence are rare and exceptional [2,121]

The figures in Tables XXXV XXXVI and XXXVII have been obtained from spleen and other organs of two cases of Gaucher's disease

TABLE XXXV

Analysis of Spleen and Serum of an Eight Year Old Boy with Gaucher's Disease (Thannhauser and Reinstein)

	Spleen	Normal Spleen
Total cholesterol	2 7 mgm	0 6–2 3 mgm
Free cholesterol	0 5	0 5 1 1
Ester cholesterol	2 0	0 –1
Total phospholipid	9 39	5 5 11 0
Sphingomyelin	0 55	0 1 0
Cephalin	1 50 "	1 6–4 0
Lecithin	3 4	3 1–4 0
Lipoid fatty acids	6 0	0–9 0
Cerebrosides	6 6	0 1–0 6 "

	Serum	Normal Serum (Fasting)
Total cholesterol	45 0 mgm	0– 60 mgm
Free cholesterol	4 0	30– 0
Ester cholesterol	105 0	0 190
Total phospholipids	91 5	5 – 50
Cerebrosides	Negative	Negative

TABLE XXXVI

Analysis of Spleen in Three Different Cases of Gaucher's Disease

Spleen	*Galactosidocerebrosides*	*Glucosidocerebrosides*
Case I	Traces	8 3 mgm
Case II	Traces	11 3 mgm
Case III	8 6 mgm	7 2 mgm

Glucosido and galactosido-cerebrosides were separately estimated (Ottenstein Schmidt and Thannhauser 9,2)

In the normal spleen 0 1 0 6 galactosidocerebroside and only traces of glucosidocerebrosides are found with the applied methods

TABLE XXXVII

ANALYSES OF ORGANS IN CASE OF GAUCHER'S DISEASE (Thannhauser and Reinstein)

	Gaucher Spleen mgm %	Normal Spleen mgm %	Gaucher Liver mgm	Normal Liver mgm %	Gaucher Kidney mgm	Normal Kidney mgm	Gaucher Heart mgm %	Normal Heart mgm %	Gaucher Lung mgm %	Normal Lung mgm
Total cholesterol	1.69	0.6–2.3	.82	1–.6	.44	1.5–.8	1.17	0.7–1.8	3.11	1–.7
Free cholesterol	0.61	0.5–1.1	0.14	0.44–0.55	0.71	0.9–1.1	0.38	0.3–0.5	1.03	0.7–1.0
Ester cholesterol	1.08	0.–1.2	2.68	1.50–2.15	1.73	0.5–1.7	1.39	0.4–1.3	.08	0.4–1.7
Total phospholipids	9.50	5.5–11.0	8.90	9.0–11.0	11.0	7.0–10.0	8.79	6.0–7.5	8.56	6.0–8.0
Sphingomyelin	—	0.7–1.0	—	0.3–0.5	1.27	0.6–0.8	0.34	0.–0.5	1.53	1.0–.0
Cephalin		1.5–7.0	0.84	3.0–5.5	6.14	0–4.0	3.44	1.5–3.0	.88	1.5–3.0
Lecithin		3.0–4.0		3.0–6.0	3.61	4.0–7.0	5.01	3.0–6.0	3.15	3.0–4.0
Total fatty acids	4.99	4.0–6	18.60	8.6–13.0	8.68	5.6–6	10.1	7.1–8.1	7	3.1–4.3
Cerebrosides	6.0	0.1–0.6	5.93	Traces	Negative	Negative	Traces	Traces	Traces	0.1–0.6

Organs through the courtesy of Dr Sidney Farber Pathological Department of Children's Hospital Boston

ETIOLOGY

Gaucher's disease is characterized by the development of an enormous number of large pale cells of a peculiar structure and content. Usually seen only in the spleen, liver, lymph nodes and bone marrow, these cells enlarge the organs in proportion to their numbers. A substantial amount of cerebrosides within these cells is found upon chemical examination. The content of the other lipids in the affected organ does not deviate greatly from the normal range.

Aghion, as well as Halliday and coworkers[3b] demonstrated that the cerebrosides in Gaucher's cells are mainly glucosidocerebrosides, while those normally present in brain are galactosidocerebrosides. In normal visceral organs like the spleen and liver the cerebroside content is extremely small and consists, according to Klenk[68, 68b] mainly of galactosidocerebrosides and only traces of glucosidocerebrosides. Ottenstein, Schmidt and Thannhauser with their quantitative colorimetric method found that in normal human organs like the lung, spleen and liver there were only 0.1-0.6 mgm. per cent of galactosidocerebrosides and only minute amounts of glucosido-cerebrosides. These authors in analyzing the spleens of three different cases of adult Gaucher's disease (see Table XXXVI) found glucosido-cerebrosides in two of them, while the third case showed glucosido- as well as galactosido-cerebrosides. In the meantime the spleen of a fourth case has been analyzed which also contained glucosido- and galactosido-cerebrosides. In organs of siblings with infantile Gaucher's disease both varieties also were present. Two facts are evident from the chemical analysis of Gaucher organs by different authors: (1) Cerebrosides normally found in greater amounts only in nervous tissue are accumulated in organs containing Gaucher cells. ( ) The nature of these cerebrosides differs from that in nervous tissue. In Gaucher cells glucosidocerebrosides prevail, while in nervous tissue only galactosidocerebrosides are present. The question to be considered is whether this deviation from the normal lipid metabolism in certain cells of visceral organs occurs as the result of a general metabolic disturbance of the intermediary metabolism or as the consequence of a cellular metabolic disorder involving only certain cells of the affected organs.

Many theories have been advanced concerning the cause of these manifestations. Gaucher, who described this disease as "epitheliome primitif de la rate," considered it a neoplastic condition involving only the spleen. However, the absence of any destructive infiltrations

metastases or cellular anarchy distinguishes Gaucher's disease from any form of malignant neoplasm

Cornil[25] recognized the fact that the cells described by Gaucher originate in the reticular mesenchymal tissue Bovaird[17] was the first investigator to doubt the neoplastic nature of the disease Schlagenhaufer[1] deserves credit for characterizing the "splenomegalies of the Gaucher type" as systemic diseases of the lymph hemopoietic apparatus This opinion was later adopted by Kraus, Eppinger[2], Waugh and MacIntosh[136] and Barat[8] According to these authors the cellular hyperplasia is the result of a storage process of an unknown substance which should be derived from blood destruction Coincidentally the occurrence of hemorrhagic diathesis should be conditioned by the thrombocytopenia following any kind of enlargment of the spleen Mandlebaum and Downey[78] first suggested that there might be a disturbance in metabolism This theory was confirmed later by the discovery of Epstein and Lorenz[4] and Lieb[73, 74] who isolated the galactosidocerebrosides from the spleen of Gaucher's disease

On the basis of these findings two different views may be discussed The first assumption, formulated and propagated by Pick, is that of a primary disturbance of the intermediary general lipid metabolism which expresses itself in an accumulation of cerebrosides in the serum and leads secondarily to a storage of this abnormal substance in the reticulum cells of the affected organs The second assumption is that of a dysfunction of the reticular cells themselves as a result of an enzymatic disturbance within the cell which leads to an increased synthesis of cerebrosides, and simultaneously to a storage of these substances within the cell The nature of the metabolic dysfunction may be suggested as an unbalance of enzymes concerned with the formation of lignocerylglucosides (cerebrosides) and lignocerylsphingosin choline phosphoric ester (sphingomyelin)

Pick believed that there is a primary general metabolic disturbance in Gaucher's disease as in other lipid diseases as a result of which cerebrosides are supplied by the serum and stored in the histiocytes as well as the reticulum cells He characterized Gaucher's disease not as a reticulo-endothelial reticular cell or histiocytomatotic disease but a histiocytic disease comparable to histiocytic storage as observed in vital staining or cholesterol feeding of animals with however, elective participation of certain histiocytic forms According to this interpretation cerebrosides are not formed in the reticular cells They are transported by the blood stream from other organs to the reticular cells, where they

are taken up and stored like cholesterol fed in excess or given by intravenous injections. The experiments of Kimmelstiel and Laas[7] seem to give some basis for this interpretation. They injected cerebrosides and found that they accumulated in the reticular cells of the spleen which had the appearance of Gaucher cells. Dworacek and Pesta[31] who also injected kerasin intraperitoneally into guinea pigs found that the substance was taken up and stored by the reticular cells but that after a time it disappeared completely. Similar experiments are reported by Christianson.[64] Neither experiment can be taken as a reproduction of Gaucher's disease where cerebrosides are found permanently within the cells. These observations only show that reticular cells can store kerasin temporarily when it is taken up from the blood stream.

The second assumption is based on the old conception of Schlagenhaufer[1, 3] that Gaucher's disease is a systemic disease of the lymph hemopoietic apparatus. Thannhauser and coworkers[12] regard the disturbance in the reticulum cells and histiocytes as a disturbance of the lipid metabolism within the cells. Based on their experiments and observations they assume that the deviation of the metabolism resulting in the formation of cerebrosides is within the reticulum cells. Cerebrosides are built in excess in these cells and retained in these cells. If this conception is correct then cerebrosides should not be found in a greater amount in the serum of patients with Gaucher's disease than in normal serum. Using chemical methods Thannhauser and coworkers[9, 12] could not find any measurable amount of cerebrosides in normal human and animal serum. In Gaucher serum like in normal serum cerebrosides are not present in measurable amounts. These observations were confirmed by the experiments of Dworacek and Pesta[31] who used physical methods. They found that kerasin has a spectrum. Spectral analysis did not reveal any evidence of kerasin in the serum. The fact that kerasin is not increased or present only in unmeasurable traces in the serum is at variance with the first assumption of Pick. If kerasin or other cerebrosides were produced by a general metabolic disturbance of the lipid metabolism and transported by the blood stream to the reticulum cells and histiocytes it should necessarily follow that these substances would be found in the serum in cases of Gaucher's disease. However chemical analysis has shown just the contrary. Cerebrosides are found only within the reticulum cell itself from which they are not transported to the organs. This finding is considered as the main proof for the conception that Gaucher's disease is an intracellular metabolic disturbance of the reticulum cell itself in which the

cerebrosides are formed and accumulated because of an intracellular enzymatic unbalance

Cerebrosides, even if not present in measurable amounts in the serum could have been derived from the stromata of red cells, which normally contain small amounts of cerebrosides and may contain larger quantities in Gaucher's disease However Ottenstein Schmidt and Thannhauser[7], analyzing dried red cells of normal persons and patients with Gaucher's disease found that red cells of normal as well as of Gaucher patients contained the same amount and the same variety of cerebrosides, namely

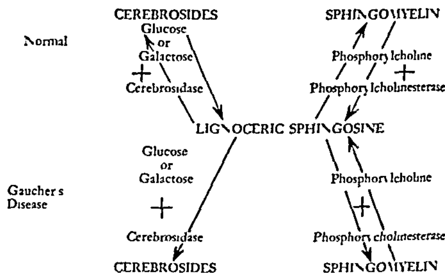


Fig 104

about 0.2 mgm per cent of galactosidocerebrosides Since the cerebrosides in Gaucher spleens and other visceral organs are mainly glucosidocerebrosides this abnormal variety of cerebroside could not have originated either from the red cells or have been supplied by the serum These findings corroborate the suggestion of Thannhauser that the accumulation of cerebrosides in Gaucher cells is an intracellular process due to a disturbance of intracellular enzymes of reticulum cells and histiocytes The cerebrosides are built and stored within the cells where they are found accumulated in Gaucher's disease

Thannhauser and Reichel[133] suggested that cerebrosidase which is not very active in the cell must be activated The activators are substances which contain an SH group

The diagram (Fig 104) attempts to picture such a hypothetical unbalance of the enzymatic action concerned with cerebroside and sphingomyelin formation Normally lignocerylsphingosin combines with cholinphosphoric ester under the influence of phosphorycholinestease to form sphingomyelin In the normal liver and spleen sphingomyelin is found in measurable quantities On the other hand lignoceryl sphingosin combines with galactose or glucose to form cerebrosides Normally this reversible enzymatic process does not lead to great amounts of cerebrosides in the liver and spleen Only minute quantities of cerebrosides are detected by analysis In Gaucher s disease the balance of enzymes which leads to cerebroside formation or cerebroside disintegration is disturbed As a result cerebrosides accumulate to such a degree in the organs involved as for example in the spleen that cerebrosides make up 4 1. per cent of the dry weight of the spleen However the amount of sphingomyelin is the same as that found in a normal spleen

A ADULT FORM OF GAUCHER S DISEASE

Clinical Course

Gaucher s disease of the adult form is an affection in which splenomegaly and pathology of the bone marrow are the most striking symptoms The onset is so insidious that usually it is difficult to ascertain when the first noticeable symptoms develop Sometimes severe dull as well as stabbing pains frequently occur in the femur as early manifestations Since fever is found often with these bone pains the diagnosis of osteomyelitis neuritis or even rheumatoid arthritis is made But the enlarged firm spleen if it is felt indicates the proper diagnosis of Gaucher s disease Spontaneous fractures and involvement of a joint are later symptoms

Sometimes the spleen increases progressively without any acute symptoms from bones or other organs until the parents or the patient himself notices the enlargement of the abdomen Eventually the spleen reaches such a size that it nearly fills the abdomen Pain in the spleen is not an early symptom Dragging sensations or sharp pains in the left abdomen are features of the fully developed clinical picture At this time the liver may be found enlarged

Abnormal patchy pigmentation on the face occasionally brings the patient to the physician in an early stage of the disease But unfortunately

the pigmentation, which may be similar to a cloasma uterinum, is not sufficiently characteristic to suggest Gaucher's disease Pigmentation on the legs as well as thickening and brownish discoloration of the conjunctiva develop usually much later The tendency to bruise very easily, to bleed from the gums or to show ecchymoses may occur in the earlier stages of the disease

The disease is characterized by a prolonged, chronic course with incidental flare ups of acute bone pain sometimes accompanied by fever In the interval which often lasts ten years and more, there are no complaints and no disturbances of important functions The patient may lead a normal life and even perform hard work One of the author's patients is a young truck driver, who has to lift heavy cases However physical efficiency diminishes in the third and fourth decade of the patient's life He may live until an intercurrent disease usually tuberculosis, shortens his life Cases have been reported of patients living until the late sixties A classification of Gaucher's disease in three stages, (1) stage of pure splenomegaly, (2) stage of splenohepatomegaly and (3) late stage with osseous and anemic symptoms does not conform to our clinical experience

There are cases observed in which anemia and leukopenia are initial symptoms together with the splenomegaly Early x ray examination in almost all cases reveals pathology of the bones especially of the femur, even at a time when no complaints suggest skeletal involvement Spontaneous fractures are rare manifestations of the disease These occur more often in older people, mostly after slight contusion Spontaneous fracture does not signify a progressive stage of the disease

The enlargement of the liver may be present also at a time when no symptoms of a generalized disease impress the examining physician Hemorrhagic manifestations such as epistaxis bleeding from the gums cutaneous ecchymosis hemoptysis and hermorrhagia may be observed at any period of Gaucher's disease Diminution of platelets causes these hemorrhages

The quiescence or progression of the disease is indicated by the general condition of the patient as well as by frequently repeated x ray films of the osseous system

Clinical Cases

Case XLVII —S B a 54 year old man (The author had the opportunity of seeing this patient with Dr Charles E Kaufman of the National

Jewish Hospital Denver Colorado The case was followed up by the late Dr Simon Baer)

The patient's family history did not reveal anything He had one brother and two sisters His father had died of pneumonia at fifty nine years of age His mother was alive at the age of eighty three

When the patient was twenty eight years old (1909) he had jaundice with cramps At that time he went to a spa in Hungary He was perfectly well until 1916 when he fell on his back and fractured two vertebræ At the same time a tumor in the abdomen was diagnosed At first this was believed to be a tumor of the kidney but further examination revealed that it was an enlarged spleen The patient's tonsils were removed in 1919 In 19 1 the right antrum was operated on In December 19 1 the patient had pleurisy with effusion on the right side and was in bed for about eight weeks From that time on he felt weak and lost his appetite A few months later (19) tuberculous peritonitis was diagnosed and the patient was in the Mount Sinai Hospital New York for six weeks Fluid was withdrawn from his abdomen and on one occasion six quarts were removed A laparotomy finally was performed and from then on the patient improved He had a hernia in the scar from this operation The patient was in bed until September 19 2

The patient then went to a tuberculosis sanatorium in Asheville N C where he stayed for nine months Examination showed tuberculous involvement of the lungs He gained twenty eight pounds at the sanatorium He returned to Cleveland where he gained ten more pounds In the meantime he developed pains and swelling on the dorsum of the right foot X rays were taken and osteomyelitis was diagnosed The patient was operated upon but no tubercle bacilli were found The patient was treated for about eighteen months Later the right knee started to swell and pained persistently although he continued to walk around

In 19 6 the patient went to the National Jewish Hospital Denver Chronic tuberculous peritonitis and tuberculosis of the right knee as well pulmonary tuberculosis were diagnosed However the diagnosis for the knee was never verified Only the sputum was positive for tubercle bacilli The patient worked at the hospital and felt well until December 1930 At that time he fell down some stairs and had a fracture of the left os ilium He was in the hospital for about six months He felt well again until he was in an automobile accident in January 1933 He complained subsequently of a marked pain in the right side of the chest but x ray examination did not reveal any signs of fracture there There were however several fractured ribs on the left side The patient had noticed for several years a brownish pigmentation on the exposed parts of his skin (face and hands) For two years he had been inclined to nose bleeds which often were quite vio

lent His chief complaint was tiredness He had no fever His appetite was fair

Upon physical examination the patient showed marked brownish pig

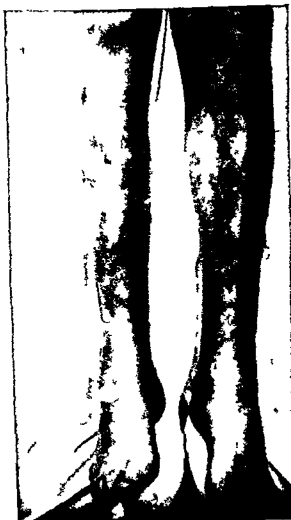


FIG. 105 Stripe like pigmentation of the legs in Gaucher's disease (case XLVII)

mentation on the face and dorsum of the hands There was a patchy pigmentation on his chest There was a triangular wedge-shaped yellowish patch on the right side of the cornea which seemed to be slightly elevated Both calves showed linear pigmentation running down from the knees to the ankles (see Fig 105) Upon first impression the pigmentation appeared like that which occurs after bleeding from varicose veins Inspection however



FIG 106 X ray of the femur of a 54 year old patient with Gaucher s disease (case XLVII) Note the thinning and the flaring of the cortex of the femur and the mottled appearance of the spongiosa

revealed that the pigmentation was not related to varicose veins or bleeding It was a very peculiar stripe like symmetric pigmentation of the lower leg which is characteristic of Gaucher s disease Examination of the lungs re

lent His chief complaint was tiredness He had no fever His appetite was fair

Upon physical examination the patient showed marked brownish pig



Fig 105 Stripe like pigmentation of the legs in Gaucher s disease (case XLVII)

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ness began at the 4th rib and extended 6 cm below the right costal margin in the midclavicular line The splenic dullness was very markedly increased beginning at the 7th interspace in the left midaxillary line and in the 6th interspace in the anterior axillary line (Fig 107) The huge rather hard spleen occupied most of the left half of the abdomen extending downward from under the left costal margin to the level of the anterior superior iliac spine and medially to the umbilicus The medial edge was smooth firm and



Fig 107 Abdomen of a seven year old child with Gaucher's disease (case XLVIII) Note the enormously enlarged spleen and the moderately enlarged liver

sharp A distinct notch was palpable in this edge 4 5 cm below the costal margin There was no splenic or hepatic bruit or friction rub The external genitalia were not remarkable except for the fact that the left testis could not be palpated There was no deformity of the bones and joints and no tenderness over the bones at this time Neurological examination revealed no abnormalities

X ray examination of the abdomen revealed large liver and spleen but no esophageal varices X ray of the long bones revealed that the lower ends

vealed dullness over the right upper lobe, anteriorly and posteriorly There was bronchial breathing over the same area with numerous crepitant consonating rales A few scattered rales were heard also over the right side The heart was normal The blood pressure was 145/80

The abdomen showed a scar between the umbilicus and the symphysis pubis with a rupture the size of a dollar (gall bladder operation scar) The left side of the abdomen seemed to be much more elevated and filled out by a large mass which on palpation could be lined out from the left costal margin to the umbilicus The tumor moved with respiration was firm in consistency and had a smooth surface This mass was an enormously enlarged spleen The liver was somewhat enlarged and palpable four centimeters below the costal margin

The reflexes were normal The patient wore a brace on his right leg The right knee was partially ankylosed X ray of his bones showed definite involvement of the bone marrow and femora with Erlenmeyer flask-like shape of the femora typical of Gaucher s disease (Fig 106)

Laboratory findings showed 85% hemoglobin 3 990,000 erythrocytes 3 580 leucocytes neutrophiles 59% with % immature forms large mononuclears 1% lymphocytes 40% Sedimentation rate was 84 The fragility test was normal The blood platelets were 49 950 Cholesterol was 147 6 Van den Bergh test 1 mgm bilirubin per 100 c c , positive delayed reaction The urine was positive for albumin Occasional white blood cells and red blood cells were found in the sediment Urobilinogen was found to be positive in concentration 1 to o bile negative

The diagnosis of Gaucher s disease was made on the basis of the clinical symptoms and x ray findings At a later date the patient died of tuberculosis The autopsy confirmed the previous diagnosis of Gaucher s disease

Case XLVIII —Z K —The author first saw this boy when he was five years old with Dr William Dameshek of Boston At this time the boy had healthy parents the father later died of coronary occlusion He had a healthy brother who had no signs of Gaucher s disease A second cousin on the father s side had a splenectomy fourteen years before questionably because of Niemann Pick s disease or Von Jaksch splenic anemia A definite diagnosis had not been made in this case at this time The cousin had recovered and was alive

Upon physical examination the boy did not appear acutely ill He was above normal intelligence and seemed bright and cheerful There was no skin pigmentation jaundice or cyanosis No ecchymoses or petechiæ were seen At this time there was no significant lymphadenopathy The eyes were normal There were no pingueculæ The lungs and heart were normal The abdomen was very large and rounded It was asymmetrical with a visible protuberance of the left upper abdomen and left flank Liver dull

mgm % indirect reaction icterus index 3 Blood Hinton Kahn and Wassermann tests were negative Three stools gave from faintly to moderately strongly positive tests for occult blood with benzidine On adrenalin test (0 c c adrenalin 1 1 000 subcutaneously) there was readily perceptible diminution in the size of the spleen accompanied by a slight increase in the number of circulating blood cells and marked increase in the white blood count The red count rose from 4 23 to 4 9 million hemoglobin from 59 to 68 / There was no significant increase in the number of reticulocytes The white count rose from 900 to 6 100 but the differential count remained unchanged and no abnormal white cells were seen in the smears

A sternal bone marrow biopsy was performed and the biopsy revealed typical Gaucher cells

Second Admission—The patient was under the author s observation the following years He played and went to school until two years later At that time his spleen became so enormously enlarged that he became short breathed He was no longer able to attend school It was decided to remove the spleen in order to relieve the boy of the mechanical discomfort caused by the displacement of other organs by the spleen It should be emphasized that the spleen was removed only for symptomatic treatment The patient was given a transfusion of his mother s blood before the operation At that time it was not known that the mother had had malaria in Palestine eighteen years ago but no recurrence since After the operation the boy began to have high intermittent fever accompanied by vomiting and slight chills The fever came regularly every fourth day Malaria parasites were found in his blood and quinine treatment was applied with full success

Laboratory studies were carried out with the following results an acid urine 1 030 specific gravity slightest possible traces of albumin no sugar normal urobilinogen The sediment was normal Blood 72 / hemoglobin or 10 grams (Sahli method) 5 100 000 red blood cells 18 300 white blood cells at entrance with 30 / polymorphonuclears 9 / eosinophiles 53 / lymphocytes 8 / monocytes The smear showed marked anisocytosis microcytosis moderate achromia Several malarial parasites were seen in the thin smear A week later the red blood count was 4 870 000 white blood count 16 800 The platelet counts were 810 000 and 8 0 000

Blood chemistry total cholesterol 157 mgm / free cholesterol 57 mgm / cholesterol esters 150 mgm / These figures were higher than those obtained upon the patient s first admission The icteric index was 9 The blood sedimentation rate was 6 mm in one hour

The patient recovered perfectly from the splenectomy as well as from the malaria The liver did not increase in size After the patient left the hospital in December 1938 he was treated with quinine and had no further malarial chills and fever In March he began to have pain in the left leg that is the left thigh The pain was migratory between the hip and the

of both femora appeared slightly deformed suggesting an Erlenmeyer flask like flaring (see Fig 108) There were no definite structural changes visible within the bone barrow

The urine varied in specific gravity from 1 030 to 1 035 and showed amounts of albumin varying from the slightest perceptible trace to 0 % There was no glycosuria and the urinary urobilinogen was normal The urinary sediment showed occasional hyaline and finely granular casts and occasional leucocytes The blood showed hemoglobin of 59%, red count 4,000 000, white count ,600 with the following differential count, band



Fig 108 Detail of the femur demonstrating the Erlenmeyer flask like appearance of the femur and the mottled appearance of the bone (case XLVIII)

forms 1% polymorphonuclears 57% eosinophiles 3% lymphocytes 37 % monocytes -% The blood smear showed marked anisocytosis poikilocytosis with many microcytes achromic cells and occasional red blood cells showing polychromatophilia The reticulocyte count was 1 4% platelets 176 000 bleeding time 1½ minutes clotting time 5 minutes (capillary tube method) The blood sedimentation rate was 8 mm in one hour (Westergren method) The blood cholesterol was 106 mgm % 43 mgm % free cholesterol 63 mgm % cholesterol esters The Van den Bergh was 0 4

mitted again to the hospital but this time with abdominal symptoms He had diarrhea and watery stools On the day he entered the hospital his stools appeared blackened and there was a question of melena At this time the laboratory reported that there was an organism of the paratyphoid group present in the stools This was later identified as a typhoid bacillus This finding was very remarkable because of the high white blood cells The author personally doubted the diagnosis of typhoid fever because of the clinical picture but the identification of the organism cultivated from the stools was made by various laboratories with the same positive results The patient recovered from the typhoid fever and was kept under quarantine for about two months Subjectively he felt quite well and played with his mates His progress in school was excellent There was no spontaneous pain in his legs but he definitely limped with his right leg X ray of the femur and pelvis in March 1940 showed that there was a complete flattening of the head of the left femur and destructive changes also of the head of the right femur The bony structure of the flattened and deformed area was markedly changed There were areas of increased and decreased density Without knowledge of the history of the patient and the diagnosis established one would interpret these bony changes as the result of Perthes disease In view of the fact that the patient was suffering from Gaucher s disease these changes in the femora had to be considered as the result of Gaucher s disease (see Fig 109) The changes in the lower end of the right femur had not altered essentially since the examination of August 1939

Blood on admission hemoglobin 78/ red blood cells 4 870 000 white blood cells 22 900 color index 0 78 differential count showed 51/ polymorphonuclear cells 1 / bands 0 5/ eosinophiles 0 5 / basophiles 26 5/ lymphocytes and 9 5/ monocytes The smear showed slight changes an occasional Howell Jolley body the platelets appeared normal The platelet count by indirect method was 844 000 A second red count was 4 0 0 000 A second white count before discharge was 35 400 Total cholesterol 140 mgm / free cholesterol 43 mgm / and cholesterol esters 97 mgm / Blood sedimentation rate was low normal on two occasions It was about 10 mm in one hour by the Westergren method uncorrected

The remarkable feature about this clinical course is that the boy had malaria and typhoid after the splenectomy Despite the fact that he had no spleen he recovered from both infections An increase of white blood cells frequently is observed after the spleen is removed In this case the white count before splenectomy was 800 After splenectomy it ranged from 15 000 to 8 000

Fifth Admission (December 1940) —The patient was admitted for an attack of diarrhea due to a paratyphoid B infection

Sixth Admission (January 1941) —The patient recovered from the paratyphoid B infection completely He was active attending school as well as

knee and accompanied by fever of 101 to 102° F for about eight days He was given codeine for the pain, and a hot electric pad was put over his leg After the pain subsided he limped for a time but was well during the following month In April the right leg began to pain him in a similar manner There seemed to be a swelling of about one-half inch in circumference of the right leg all the way between the hip and the knee There was also heat and redness The pain was so severe that morphine had to be given The second attack was more severe than the one for which he had come originally to the hospital During the month of April x ray therapy was applied to the right leg The results were good in respect to the pain Subsequent x ray photographs of the thighs showed rather marked bone changes

Third Admission (August 1939) —The patient was again admitted to the hospital in August 1939 Physical examination showed that the legs appeared entirely normal The hip and knee motions were unrestrained The right leg however, was held in flexion on the thigh and in the lower thigh near the knee, there was a slight suggestion of heat and very slight tenderness on firm deep pressure although percussion of the bone at its lower end caused no peculiar distress The motion in the knee joint was normal There was no swelling about the joint or evidence of fluid However when an attempt was made to rotate the thigh in the hip socket there was muscular spasm and discomfort in the lower end of the thigh

The following laboratory studies were carried out at this time Urine amber, clear acid specific gravity of 1 031 no albumin no sugar, normal urobilinogen no urobilin sediment not remarkable Blood 67% hemoglobin or 9 5 grams red blood cells 4 430 000 white blood count 28 800 color index 0 76, differential count, 6 5 polymorphonuclears 3% eosinophiles % basophiles lymphocytes 26% monocytes 6 5% The smear showed moderate changes in sizes and shape The platelets appeared increased in number some were large in size The second white blood count on the 5th day following admission was 28 300 with the following differential 56% polymorphonuclears 3% eosinophiles -% basophiles 30% lymphocytes and 9% monocytes The blood sedimentation rate at entrance was normal only 10 mm in one hour

X ray examination of the femora showed at this time definite periosteal reaction at the medial and posterior borders of the lower end of the femur about 6 cm proximal to the knee joint and extending for a length of about 10 cm This was probably more marked and more bony than at the previous examination and was probably secondary to the radiation There was also further resorption of the medullary canal of the lower end of the femur about 1½ cm proximal to the epiphysis This area was roughly quadrilateral in shape and measured about 5×3 cm In addition the Erlenmeyer flask appearance of the femora was more marked than before

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Fourth Admission (January 1940) —In January 1940 the patient was ad

Seventh Admission (March 1943)—Repetition of throat infection with high fever The lymph nodes on both sides of his neck were much larger than usual Blood showed 68 per cent hemoglobin red blood cells 4 110-000 color index 0 83 white blood cells 4 000 16 per cent bandforms 48 per cent polynuclears 2 per cent eosinophiles 23 per cent lymphocytes 10 per cent monocytes platelets 979 000 The swelling of the lymph nodes decreased but they still were enlarged at his discharge

Eighth Admission (May 1943)—The boy had acute pain and swelling of his left femur and fever X ray treatment alleviated the pain The fever disappeared during the treatment

Ninth Admission (August 1943)—Two days before the patient's admission he was pushed by his brother and he fell on a curb stone hitting his right leg below the knee The pain became so excruciating that he was unable to walk *X ray Examination*—There is tremendous ballooning of the lower half of the left femur as had been observed previously There is no fracture The x ray shows that the right tibia now is involved also in the process of Gaucher's disease

Tenth Admission (April 1944)—He was in good health and active in play since his last admission Two days ago he had an acute severe pain in his right thigh with fever There was no trauma this time *X ray Examination*—There are some soft matted shadows visible in the midshaft of the right femur which may represent active bone marrow changes These changes are higher up than the obvious swelling above the knee joint X ray therapy relieved his pain

The boy has been seen repeatedly since as an ambulatory patient He has developed well He is now 15 years old 69 inches high and weighing 140 pounds He does very well in school His liver is extremely large extending 5 fingers below the costal margin The lymph nodes in his neck are small but firm There are no lymph nodes palpable in his axillæ but some of almond size are present in his groins The x ray pictures of his lungs show no tuberculous or other involvement Hemoglobin red and white blood cells and platelets are normal

On January 8 1947 he noticed that the left knee was swollen but had no pain After a few days rest the swelling disappeared

On February 7th 1947 his left tibia suddenly caved in and has remained bowed since X ray examination revealed a spontaneous fracture of the left tibia (Fig 110) This fracture may be compared to Loeser's zone (transformation zone) in osteomalacia The left lower tibia apparently became so involved in the Gaucher process that the bone became malacic and softened The spontaneous fracture occurred without pain X ray treatment so far has not accelerated the callous formation The patient uses crutches His general condition has remained good

playing outside though he limped slightly He was tripped while skating and fell and struck his side The next day he had an attack of severe pain in his left hip and femur and could not extend his leg or walk on it His temperature reached 103° F Later he developed a sore throat Throat culture showed diplococcus of the enterococcus group and streptococcus hemolyticus, blood culture was negative blood smear showed nothing abnormal



Fig 109 Pelvis of a seven year old child with Gaucher's disease (case XLVIII) Note the cyst in the right femur and pelvis The changes of the femur head are similar to those found in Perthes disease

X ray *Examination* —There is now complete fragmentation of the heads of the femora The fragment of the right femur is somewhat dislocated away from the acetabulum The lower end of each femur is distended (flaxed) to an extreme degree now There is no evidence of any active process of bone destruction X-ray therapy of his left hip and femur was as effective as it had been previously when the right femur was painful and swollen and treated by x ray

time on the patient apparently was in good health until early in 1939 She entered the hospital from the out patient department where she had been followed for the previous year and a half She had a two year history of recurring migratory joint symptoms affecting the hands wrists elbows hips knees and feet The joints would become swollen hot and painful with limitation of motion Symptoms would persist for a day or longer and then would subside only to appear in another group of joints The adjacent soft tissue also would become swollen Between episodes the joints would appear perfectly normal with no tenderness or limitation of motion Active use of these joints and exposure to cold would tend to make the symptoms appear The picture was not unlike that of rheumatic fever

On *physical examination* the findings of note were a rough grade II systolic murmur in the pulmonary area a slight anemia of 3 7 to 4 0 million red blood cells and a white blood cell count of 5 000 to 6 000 which was noted throughout the course of the illness X rays of the chest showed the heart slightly enlarged downward and to the left and an electrocardiogram disclosed a delayed A V conduction time X ray of the hands in February 1940 showed narrowing of the interphalangeal joints without erosion suggestive of early atrophic (rheumatoid) arthritis Nine months before admission small subcutaneous nodules were noted on the posterior aspects of both arms lasting several days and leaving ecchymotic spots as they subsided Tenderness in the left upper quadrant was noted by several observers The spleen however was not felt

During the year previous to admission the patient had frequent sore throats and episodes of epistaxis She gave up work entirely in the last half of this period and rested at home with considerable relief from symptoms During this time her appetite was poor she lost seven pounds and there was a tendency to bruise easily

Physical examination on admission showed a well developed and well nourished girl who did not appear ill The heart did not appear enlarged to percussion or palpation There was a soft systolic murmur at the apex and a rather harsh systolic murmur in the pulmonary area There was a loud second sound The lungs were normal The abdomen showed an area of tenderness on deep palpation just lateral to and above the umbilicus on the left side A moderate enlargement of the metacarpophalangeal joints of both hands with soft tissue swelling over the dorsum of the hands and a spindle shaped appearance of the digits were noted The joints were not hot or painful and there was no limitation of motion All other joints were normal There was a long scar on the lateral aspect of the left thigh and a smaller scar on the lower medial aspect of the right thigh Over the apex of the root of the left upper canine tooth was a small acutely tender nodule Numerous small areas of ecchymosis were scattered over the body and extremities

On September 5, 1947 the callous formation was found to be good. The patient walks without crutches. There is no pain, no fever.

Case XLIX.—R. C., a [illegible]1-year old unmarried girl was observed in 1941 at the Peter Brent Brigham Hospital. The case was reported by J. Reed and M. C. Sosman because of its unusual x-ray findings[114].

This patient was the third of a family of six children, three brothers and three sisters, without history of familial disease. As a child the patient had

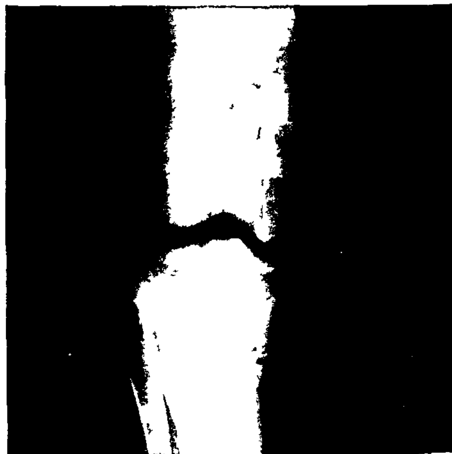


Fig. 110. Spontaneous fracture of the left tibia (case XLVIII)

measles, whooping cough, chickenpox and scarlet fever. A tonsillectomy was performed in 1924 at the Children's Hospital. In 19[illegible]9 she entered the Carney Hospital where she was operated on for osteomyelitis of the lower third of the left femur. In 1932 drainage of osteomyelitis of the lower third of the right femur was done at the Boston City Hospital. Two years after the second operation the wound stopped draining and healed. From that

in the radii consisted of expansion of the medullary cavities in the upper thirds A film of the abdomen showed a considerably enlarged liver and a moderately enlarged spleen although the spleen could not be felt on physical examination



Fi 111 Atypical bone lesion in the femur in Gaucher's disease (case XLIX)

On the strength of the x ray findings bone biopsy was recommended and on the fifteenth hospital day biopsy of the humerus was done Sections

"*Laboratory data* while the patient was in the hospital were as follows Urine concentrated to 1 012 with occasional white blood cells in the non catherized specimen No casts or Bence-Jones protein were found Red blood cells were 3 900 000, hemoglobin 9 6 gm per cent, hematocrit reading 33 per cent, sedimentation rate 18 mm per hour on one occasion and 15 mm per hour on another, white blood cells 5 000, 65 per cent neutrophils 26 per cent lymphocytes 3 per cent monocytes Red cells showed marked variation in size with some chormatophilia Reticulocytes were 8 per cent Blood chemistry non-protein nitrogen 6 mgm per cent, cholesterol 149 mgm per cent, protein 7 gm per cent albumin 4 5 gm per cent globulin 2 5 gm per cent, calcium 4 9 milli equivalents per liter phosphorus 1 1 milli equivalents per liter, alkaline phosphatase 1 8 Bodansky units Stool was negative Formol gel and Takata Ara tests were negative Blood clotting time was eight minutes

The patient was seen first in the x-ray department a year and a half before admission to the hospital when chest films were taken At that time there was a hyperactive beat and a slight enlargement of the left ventricle A peculiar mottling of the portion of the humeri seen in the chest films was noted, and the films of the humeri were requested at this time but the patient did not return to the department Six months later films of the hands and wrists were taken and a narrowing of the interphalangeal joints without erosion or destruction was noted

'During the patient s hospital stay extensive x ray studies of the bones were made The findings were somewhat at variance with those commonly described in Gaucher s disease Films of the spine were essentially normal A rather fine granular appearance was noted in the skull and pelvis The *most marked changes were in the femora (Fig 111) and humeri* (Fig 11) with similar but less pronounced changes in the tibiae and radii and no involvement of fibulae and ulnae The humeri (Fig 112) presented an unusual appearance with multiple, small irregular defects in the cortex of the shaft The lesions were not circular and clean-cut as in multiple myeloma but were more elongated and oval without bone reaction around them The appearance was more that of a spreading apart of the trabeculae than of a destruction of bone The lower (distal) thirds showed an apparent expansion of the medullary cavity simulating a proliferation of the bone marrow expanding the bone The most striking changes were in the lower thirds where there was a widening of the bones and marked thickening of the cortex rather than the thinning usually observed The upper half of each femur (Fig 111) had a hollowed tunneled out appearance resembling somewhat the changes seen in caisson disease involving this bone The femoral heads showed coarse trabeculae and small cysts The changes in the tibiae were similar to but less marked than those in the humeri and growth arrest lines were present in the upper ends The only changes seen

Clinical Features

Incidence —Gaucher's disease usually is regarded as a rare affection However as Cushing and Stout[29] remarked the clinical features are not sufficiently known to be always recognized In 1926 Pick[10] collected the reports of 39 authentic cases Since then many new cases have been found Hoffman and Makler[60] listed 89 cases in 19 9 although several of these were not accepted as authentic according to standards set by Mandlebaum[77] and Pick[107] There are now about 00 cases of this disease recorded in the literature[13, b 2, 31, 47b, 49a, 34b, 5, 53, 7, 7b, 7, 79, 96, 100, 100b, 100c, 11 b, 118b, 119, 119b, 1 4b, 1, 1 9, 1 0, 131, 131, 134a, 137, 140] Many more have been observed without publication

Distribution —Gaucher s disease is found widely distributed in the countries of Europe and America Spackman and Mackie[130] have reported a case from India The author knows of three siblings of Japanese origin with Gaucher s disease (Dr Tom Fujiwara personal communication) About one third of the reported cases have been observed in the United States

Race and Sex —This disease occurs among both white and colored people Its frequency among the Jews has been mentioned in all the publications While females are more affected than males there seems to be no definite predominance of either sex in the disease

Familial Occurrence —Collier[27] and Bovaird[17] early observed the occurrence of Gaucher s disease in siblings Brill and Mandlebaum[1] reported five out of six brothers and sisters with the disease Oberling and Woringer[96] described four infantile cases in siblings Dimond[1] noted the occurrence of Gaucher s disease in several generations of one family The author now has observed repeatedly that Gaucher s disease not only occurs in brothers and sisters but is also present in members of different generations of one family Groen and Garrer[5 b] discuss the mechanism of heredity The authors suggest dominant sequence of heredity Their assumption is not entirely convincing

Age —The two different forms of Gaucher s disease involve two different age ranges The acute infantile form starts during the first six months of the infant s life Death usually results in the second year The adult form may make its appearance in childhood adolescence or later life The exact age at which the chronic adult form begins is difficult to determine because of the insidious onset of the disease In Cushing and Stout s[29] series 58 per cent of the patients developed symptoms during the first decade of their life The remainder of the cases

revealed characteristic Gaucher cells Abdominal films as well as films of the humeri and femora of both parents and 5 siblings were taken No evidence of Gaucher's disease was found in any of them'



Fig 112 Atypical lesion in humeri in Gaucher's disease (case XLIX)

The patient has been later under the continuous observation of Dr H Brugsch of the Pratt Diagnostic Hospital since 194- She is married and has a child which up to now is normal There is no essential change in her clinical features

sionally surface irregularities can be observed The mass of the spleen may drop into the left lower quadrant by a torsion of its pedicle and thus it may be difficult to decide whether it is a spleen or a tumor Pain which sometimes is very intense may result from local perisplenitis from the distension of the splenic capsule or from a strain on its pedicle The character of the splenic ache may simulate colicky pain Partial ileus may ensue from pressure on the colon The enormous mass of the spleen displaces the abdominal organs and presses the diaphragm so high that shortness of breath results from the slightest exertion Shortness of breath may be the first sign which induces the patient to consult a physician There is one case on record where spontaneous rupture of the spleen occurred[66] Splenectomy may be indicated, not to prevent the progression of the disease but to relieve the threatening symptoms of abdominal displacement and shortness of breath However patients usually suffer little discomfort despite the enormous enlargement of the spleen and liver Most of them are able to participate in sports and attend to their business activities

Liver — The liver usually is not involved as extensively as the spleen Some patients have been described with fully developed symptoms without noticeable enlargement of the liver In other patients the liver may be considerably increased in size However there is always a disproportion between the size of the liver and the spleen There are no additional clinical symptoms of a chronic liver disease A slight transient jaundice has been observed as an exception in only a few cases There is no ascites Sometimes abdominal colicky pains are misinterpreted as gall stone colic An operation, if it is erroneously performed discloses a large liver with a grayish brown surface but no remarkable increase of connective tissue In later stages however the connective tissue which is increased may stimulate liver cirrhosis (Teium[13]) Numerous cerebroside containing reticular cells and histiocytes, which are present in the liver explain the increased volume of the liver The connective tissue is the result of scar tissue replacing Gaucher cells or it may be due to local irritation The Gaucher liver is never as firm to the touch as a true cirrhotic liver The pigmentation of the skin occurring with the liver enlargement may suggest hemochromatosis Biopsies of the skin may show the presence of hemosiderin (iron) in addition to true melanin The blood sugar curves are normal The liver function tests usually do not show impaired liver function Galactose test bromsulphthalein cholesterol cholesterol ester ratio are all mostly normal Takata Ara test is negative Serum bilirubin is slightly increased Van den Bergh

were distributed about evenly in patients between the ages of 10 and 30 years of age. Sixteen cases were observed in patients over 30 years of age, the oldest of which was 56. The oldest case on record was 79 years old[100b]. In Hoffman and Makler's[70] series the onset occurred most frequently in children under 5 years of age. Since the predisposition is no doubt congenital, the disease may manifest itself at any age. It is probably doubtful whether all the infantile cases which were reported as Gaucher's disease, really belong to this category and not to that of Niemann-Pick's disease. The diagnosis of the acute infantile form of Gaucher's disease should only be accepted in cases where there has been a chemical analysis and isolation of cerebrosides.

Predisposing Diseases.—Acute infections appear to activate the disease and to hasten its progress. Ewing in the 1928 edition of "Neoplastic Diseases" states that Gaucher's disease has many features of an atypical tuberculosis. Although tuberculosis occurs frequently and simultaneously with Gaucher's disease, it should be considered only as a complication and not as a direct etiological factor in the disease. Some investigators believe that a virus may irritate the reticular cells and cause tumor-like alterations. This conception also has not been verified by any evidence.

General Appearance.—The patients usually do not give the impression of being sick. During an acute and excruciating attack of bone pains, however, they appear haggard and drawn even after the disappearance of the accompanying fever. It is erroneous to believe that all patients with Gaucher's disease look pale. Many are not anemic. Pigmentation, usually not observed in the younger age group, is of a diffuse sallow color if it occurs; pigmentation is discussed on a later page. The abdomen is in some instances distended by the enlarged spleen.

Spleen.—The enlargment of the spleen originally gave the disease its name, "epithelioma primitif de la rate." The size of the spleen increases slowly. Sometimes it can be felt only one finger below the left costal margin. At other times a large splenic mass crosses the midline to the right side and reaches far below the umbilicus, extending down into the pelvis. The upper border of splenic dullness may be found by percussion to extend as high as the fifth rib. The spleen, however, may remain of moderate size, even one case being reported without splenomegaly[8], and the principal symptoms of the disease are the results of skeletal involvement. Usually the contours of the enlarged spleen may be seen through the abdominal wall. The left side of the abdomen is protruded. The surface feels firm and moves with respiration. Occa-

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a special skeletal or osseous form from the usual clinical syndrome of this disease

Brill Mandlebaum and Libman[77] were the first investigators who at autopsy discovered the presence of Gaucher cells in the bone marrow At present the bone marrow involvement can be diagnosed by means of x ray because of the simultaneous patchy decalcification of the long bones and by sternal bone marrow puncture

X ray Changes in the Bones —X ray examination (Figs 106 and 108) reveals the following main changes in the bone structure decalcification bone sclerosis bone absorption and destruction and deformities in the outlines of the bones especially in the femur and the vertebrae In the early stages of the disease the structure of the femur (patchy decalcification) looks like cotton wool in the x ray film This appearance which has been described sometimes as moth eaten or worm eaten in the literature is not solely characteristic of Gaucher's disease In the early stages of the disease a characteristic and even pathognomonic deformity of the distal end of the femur develops, giving it the contours of an Erlenmeyer flask (Fig 108) The waistline above the condyles of the femur disappears because the thinned cortex of the bone seems to be expanded and inflated in this area probably as the result of the replacement of the marrow by Gaucher cells Decalified areas which simulate cystic involvement similar to the cystic decalification of the bones in eosinophilic xanthomatous granuloma are found rarely in Gaucher's disease (Fig 109) If they are present they are located in the upper part of the femur around the hip joint which sometimes may be destroyed and in the pelvis

Osteosclerotic appearance of the bones[140b] similar to that in erythroblastic anemia may be found occasionally in the radius and ulna The most impressive bone destruction as well as that of the most serious consequences occurs in the vertebral column in which one or more bodies of the vertebrae may be involved (Fig 99) Melamed and Chester[81] described a case with an outstanding destruction of the vertebral column There was a marked demolition of several vertebrae The bodies of the fifth and seventh dorsal vertebrae were collapsed to one third their usual size They were somewhat elongated extending slightly beyond the border of the contiguous vertebral bodies The body of the ninth dorsal showed marked absorption The bodies of the eleventh dorsal and first lumber vertebrae also were collapsed to about one third of their normal size The space between the twelfth dorsal and first lumbar

reaction shows indirect bilirubin 1-3 mgm. Mandlebaum, Berger and Lederer[77a] reported a case of Gaucher's disease complicated by hemolytic jaundice. Multiple telangiectases of tongue and buccal membrane were observed in a 68-year old woman with Gaucher's disease[13].

Lymph Nodes.—Generalized lymphadenopathy is not a characteristic feature of this disease although it occurs in the younger age group. Scattered Gaucher cells are found in these nodes at biopsy. The lymph nodes were not palpable in twenty cases of Cushing and Stout's[73] series. A few small nodes were reported in nine cases. Out of fifteen cases observed by the author enlarged lymph nodes in the neck and axilla were found only in two youngsters. The lymph nodes were not enlarged in adults.

In contrast to these cases are those of the acute infantile form of Gaucher's disease, where the peripheral lymph nodes always are involved. At autopsy the deep abdominal lymph nodes and less frequently the thoracic nodes are found involved. A biopsy of a lymph node sometimes is very helpful for verifying the diagnosis. A bone marrow biopsy is more advisable, however, for routine purposes.

Bone Symptoms.—The onset of the disease sometimes is marked by severe pain which is found especially in the thigh and radiates down the calf. The patients' complaints are mostly misinterpreted as rheumatic pains. Swelling of the joints may also be an occasional symptom. However the joints usually are involved secondarily in a later stage of the disease as a result of bone destruction. The so-called rheumatic pains are caused by the widespread Gaucher cell formation in the marrow. They are probably also due to small local bleeding in the marrow. The pain usually occurs after some mild local trauma. The fact that this kind of pain may be present in attacks with elevated temperature is not widely known. The patient feels prostrated and looks severely ill and dehydrated during the spell. The author knows of only one other disease with bone involvement, which produces similar excruciating pains and elevated temperature namely, a Ewing tumor. The Gaucher patient who recovers completely after the attack, is again able to perform his daily tasks. The aches and pains may occur also in less severe degree without fever.

Physicians who have observed patients with Gaucher's disease over a long period of years are aware that besides the enlarged spleen the involvement of the skeletal system is the most outstanding clinical symptom of the disease. The author, therefore, does not approve separating

vertebrae was obliterated There was some absorption and narrowing of the body of the fourth lumbar vertebra

In most of the reported cases the affection of the vertebral column is restricted to one or two vertebral bodies In these cases the condition simulates a tuberculosis destruction rather than a neoplastic metastasis Pott's symptom, which usually is characteristic of tuberculous destruction of a vertebra, also may be found in the bones as a result of destruction by Gaucher's disease In contrast to tuberculous destruction of the vertebrae, the intervertebral disk and the surface of the neighboring vertebrae are not involved Despite the fact that cases exist in which there is a collapse of the vertebra, such as the one just mentioned, symptoms of a lesion of the spinal cord have not yet been reported in Gaucher's disease Spontaneous fractures of the long bones of the skeleton are observed, especially of the head of the femur

The spontaneous fracture in Case XLVIII manifested itself by spontaneous bowing of the tibia without any pain The x-ray picture (see Fig 110) showed a zone of incomplete fracture comparable to 'Loeser transformation zones" in osteomalacia In this case, however, the infiltration with Gaucher cells caused the "transformation zone" and consequently the incomplete fracture Bone lesions in unusual areas like the skull[100] and mandible[7 b] are described

Joints—Gaucher's disease occasionally may simulate polyarthritic attacks such as rheumatic fever or rheumatoid arthritis. As has been stated already, the pains and aches, which the patient feels in the joints as well as in the muscles and bones, result from the involvement of the bone marrow in Gaucher's disease Occasionally there may be swelling around the joints This completely disappears after the acute attack No scarring remains, nor is there shrinkage of the periarticular tissue The joints however, become involved secondarily in Gaucher's disease if the surface of the bone itself becomes destroyed by the osteolytic process The hip and knee joints occasionally show such involvement of the joint Spontaneous fractures may occur in the vicinity of these joints

Pigmentation—The pigment of the skin in patients with Gaucher's disease has been demonstrated to be true melanin The cause of the increase of melanin the normal skin pigment on some parts of the body of Gaucher patients is not known Pigmentation is not found in all instances It occurs rarely in children under ten years of age Spots of pigmentation which are observed usually in the adolescent period, become darker as the patient grows older

Different kinds as well as different areas of pigmentation have been reported. Most authors describe a brownish tan pigmentation or chloasma uterinum like patches on exposed parts of the body, such as the face (Fig 113), neck and hands. A symmetrical pigmentation of the legs (Fig 105) was reported recently by Groen and his associates[31] who described this circular pigmentation as extending from the instep to the knees. While the lower margin of the pigmented area was straight and well defined, the upper border showed stripe like projections with normal skin between them. The skin, which was slightly atrophic and glossy, varied in color from leaden gray to dark brown. There were no varicose veins but occasionally there were small ulcers. Similar pigmentation was observed in the case of the patient case XLVII.

Groen's[31] patient also showed pigmentation of the mucous membrane of the mouth. Therefore a diagnosis of Addison's disease or hemochromatosis was ventured. A biopsy of the mucous membrane revealed melanin but no iron. Pigmentation of the mucous membrane is a very rare occurrence in Gaucher's disease. It occurs only in cases of destruction of the adrenal medulla. A destruction of the adrenal medulla could be caused by tuberculous caseation, by siderosis producing scar tissue from the deposit of iron-containing pigment or from lipid cells accumulating in the medulla of the adrenal gland and leading to scar tissue as observed in Niemann Pick's disease. Since in Gaucher's disease of adults Gaucher cells do not accumulate in the adrenal, this last possibility, accumulation of lipid loaded cells in the medulla of the adrenal, is limited to infantile Gaucher's and to Niemann Pick's disease. Therefore a mucous membrane pigmentation in Gaucher's disease which is exceptional, probably has not been caused by a destruction of the adrenal medulla by the Gaucher cells. It may, however, have resulted from a deposition of iron in the adrenal medulla since hemosiderosis is always found simultaneously with Gaucher's disease or from a complication with tuberculosis.

Eyes.—Wedge shaped thickenings of the conjunctiva, which extend symmetrically from their bases at the corneal margin to their apices at the inner and outer canthi, usually develop in the second decade of the patient's life (Fig 113). Their growth is very slow. Their color is brownish and later changes to ochre like. These thickenings, which resemble pingueculae, may escape observation and must be looked for in good daylight. East and Savin examined histologically the pingueculae of a case of Gaucher's disease[31]. They found Gaucher cells in the pinguecula. Unfortunately they did not examine the kind of pigment which caused the brownish color of the pinguecula.

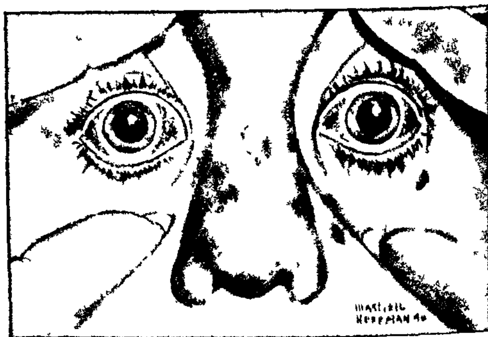


FIG 113 —Gaucher s disease Wedge shaped thickening and pigmentation of the conjunctiva on both sides of the pupil Note patchy pigmentation on and around the nose

Chester[81]) The size of the red cells may equal that of the macrocytic type but only in the terminal stage of anemia[4 b] Leukopenia may not be present in the early stage but rarely is lacking at the height of the disease The differential count shows nothing unusual Graham and Blacklock[43] found a small percentage of myelocytes in the blood In the case described by Melamed and Chester[81] myeloid metaplasia was found in the liver which contained cells of the myelopoietic and erythropoietic series This condition may occur only in rare instances as a result of a severe insufficiency of the bone marrow Gaucher cells have not been demonstrated in the peripheral blood stream with the exception of one doubtful case reported by Diguglichow This is in contrast to Niemann Pick s disease where Niemann Pick cells cells of foamy structure as well as abnormal reticulum cells may be found (Poncher[110] Baumann and associates[9]) This distinction is valuable for the clinical differential diagnosis of the two diseases especially in cases of infants Thrombocytopenia is present in almost all cases of Gaucher s disease Hemorrhagic tendencies on the other hand are mentioned only in about 50 per cent of the reported cases Hemorrhages petechiae as well as bruises may be observed on the skin Bleeding from the mucous membranes occurs later in the disease Epistaxis is the most common form Bleeding may occur also from the gums stomach and bowels Hemorrhages from the uterus as well as bloody effusions in the pleural cavity (Brill and Mandlebaum[19]) and in the pericardium have been reported

Bleeding coagulation as well as prothrombin times are normal The fragility of the erythrocytes against sodium chloride solutions also is in normal limits There is only one case reported where acquired hemolytic anemia complicated Gaucher s disease Melamed and Chester s[81] case showed an increased resistance of the red blood cells to sodium sulphate solution (Hamburger s test) After splenectomy the low platelet count rises to normal sometimes to high values The leukopenia also disappears immediately after splenectomy and even leucocytosis is observed A marked rise occurs simultaneously in the eosinophiles

Serum Chemistry —The most important problem concerning Gaucher s disease is whether there is an increase of the cerebrosides in the serum The normal serum does not contain any measurable amounts of cerebrosides The author and his associates were unable to find cerebrosides in measurable quantities in the serum in Gaucher s disease The same negative findings were obtained by spectrophotometric determinations Cerebrosides are found increased only in the organs involved in Gaucher s disease

In cases, where this brownish thickening of the conjunctiva is found simultaneously with bone changes and enlarged spleen, the diagnosis of Gaucher's disease is unmistakable. Brill[18] thought that the brownish wedge shaped thickenings of the conjunctiva are pathognomonic of the disease. Small hemorrhages may occur in the retina in a stage of the disease where a hemorrhagic diathesis becomes evident. Groen and his associates[11], who observed myopia in all of their cases, considered it a constant symptom of Gaucher's disease. However, myopia has not been found in many cases observed by the author, nor has it been reported as a characteristic symptom in the literature by other investigators.

Endocrine Glands.—The reticulum cells of the endocrine glands are not involved in the adult form of the disease (see section on pigmentation). Only one exceptional case is reported[13,14] where Gaucher cells in the posterior lobe of the pituitary and in the hypothalamic region were found at autopsy of a 50 year old woman. There were no clinical symptoms referable to these lesions.

While retardation in growth may be found in the first ten years of the patient's life, usually it is overcome in the adolescent period. Although mental retardation has been reported in some cases, most of the patients with Gaucher's disease described in the literature are mentally normal and even very intelligent. The patients observed by the author were all mentally highly developed.

The basal metabolism is normal. Deviations in the metabolism *which are reported occasionally are not connected with the disease.*

Blood.—The stromata of the red cells contain normally 0 [illegible] mgm per cent cerebrosides. There is no increase of cerebrosides found in the stromata of red cells in Gaucher's disease. The composition of the white blood cells is not changed. The replacement of bone marrow by Gaucher cells may result in anemia, leukopenia and thrombocytopenia, features otherwise found in myelophthisis occurring in aplastic anemia or in cases of anemia where the bone marrow is generally replaced through neoplastic tissues. The anemia is of the microcytic type with an average erythrocyte count of 3 000 000 to 4 000 000 with about 50 per cent hemoglobin. Occasionally the erythrocyte count and hemoglobin suddenly drop to such a low level in the terminal stage of the disease that the blood condition can be regarded as a factor determining the fate of the patient. The terminal anemia may be the result of the hemorrhagic condition which occurs simultaneously with the thrombocytopenia[30]. Nucleated and stippled red cells are found in a few cases (Melamed and

Chester[81]) The size of the red cells may equal that of the macrocytic type but only in the terminal stage of anemia[4, 6] Leukopenia may not be present in the early stage but rarely is lacking at the height of the disease The differential count shows nothing unusual Graham and Blacklock[43] found a small percentage of myelocytes in the blood In the case described by Melamed and Chester[81] myeloid metaplasia was found in the liver which contained cells of the myelopoietic and erythropoietic series This condition may occur only in rare instances as a result of a severe insufficiency of the bone marrow Gaucher cells have not been demonstrated in the peripheral blood stream with the exception of one doubtful case reported by Diguglichow This is in contrast to Niemann Pick's disease where Niemann Pick cells cells of foamy structure as well as abnormal reticulum cells may be found (Poncher[110] Baumann and associates[9]) This distinction is valuable for the clinical differential diagnosis of the two diseases especially in cases of infants Thrombocytopenia is present in almost all cases of Gaucher's disease Hemorrhagic tendencies on the other hand are mentioned only in about 50 per cent of the reported cases Hemorrhages petechiae as well as bruises may be observed on the skin Bleeding from the mucous membranes occurs later in the disease Epistaxis is the most common form Bleeding may occur also from the gums stomach and bowels Hemorrhages from the uterus as well as bloody effusions in the pleural cavity (Brill and Mandlebaum[19]) and in the pericardium have been reported

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The figures for total cholesterol are normal or low normal. The ratio of cholesterol to cholesterol ester depends on the condition of hepatic parenchyma but usually is normal (Pichman[98]). The total phospholipids as well as lecithin and cephalin are normal or low normal. Neutral fat is normal. No case has been described with hyperlipemia. The total lipids are rather low than high.

The serum figures in Table XXXVII were obtained in the case of patient XLVIII (for clinical course, see previous pages).

TABLE XXXVII

	Before splenectomy	After splenectomy
	mgm %	mgm
Total cholesterol	100	145.0
Free cholesterol	26.7	40.0
Ester cholesterol	73.3	105.0
Total phospholipids		95.1

Table XXXVIII shows the figures of serum lipids of a twenty two year old girl with Gaucher's disease and exhibiting enlarged spleen and bone involvement.

TABLE XXXVIII

	mgm %
Total cholesterol	137.0
Free cholesterol	55.5
Ester cholesterol	81.5
Total phospholipids	119.3
Sphingomyelin	16.0
Total fatty acids	27.0
Molisch reaction	negative

The fact that cerebrosides are found only in the organs involved in Gaucher's disease but not in the serum is significant for the suggested etiology of the disease. Cerebrosides are built and stored as a result of a deviation of the intracellular metabolism. The bilirubin value usually shows a slight increase of the indirect bilirubin reaction (Van den Bergh) 0.5-2.0 mgm per cent. The direct bilirubin reaction is negative. Non-

protein nitrogen is normal Calcium and phosphorus values are normal Phosphatase in the serum is high normal or slightly increased 4 to 10 Bodansky units

Urine—An increase of urobilin and urobilinogen is occasionally found No bilirubin or abnormal pigments are present An increase of bilirubin (indirect) however is sometimes present in the serum

Diagnosis

The onset of the adult form of Gaucher s disease is so insidious that the diagnosis is not made at the onset of the disease The so called rheumatic pains diffuse pains in the bones which occur in a patient with an enlarged spleen should suggest x ray examination of the bones A film of the femur especially should be made The flaring of the distal part of the femur as a result of the thinned and distended cortex the so called Erlenmeyer flask appearance is one of the first and rather pathognomonic signs of the disease While medullary absorption the mottled cotton wool like appearance and the thinning of the cortex of the bones as osteosclerotic signs in the x ray picture are not pathognomonic of Gaucher s disease these changes together with Erlenmeyer flask like deformity of the expanded femur are of great diagnostic value Cortical and periosteal thickening rarely occurs In those cases where it is present it is the result of secondary changes following compression and spontaneous fractures

The diagnosis of Gaucher s disease is suggested by the following clinical syndrome the disproportion between the enormous enlargement of the spleen and the moderate enlargement of the liver the absence of striking signs of portal congestion or obstruction ascites and visible jaundice the presence of patchy cloasma like skin pigmentation and brownish wedge shaped thickening of the conjunctiva This syndrome is however unfortunately not fully developed in the early stages of the disease The physician is in the earlier stages confronted with a patient who exhibits a large spleen leukopenia a low number of platelets and sometimes tendency to hemorrhages Since leukopenia and a low number of platelets may occur together with a large spleen in a considerable number of other diseases the blood picture is not of much help in the diagnosis of Gaucher s disease

Bone marrow biopsy should be performed in all cases where a diagnosis of Gaucher s disease is being considered The choice between

bone marrow puncture and bone marrow biopsy depends upon the personal experience of the physician While it is possible to visualize the characteristic Gaucher cells by both methods, the bone marrow biopsy also permits tissue staining which is very helpful for the differential diagnosis The splenic puncture should be abandoned as a routine method in favor of the bone marrow puncture However, there may be exceptional cases where a splenic puncture is necessary

In the fresh specimen a very large (90 micra average), rather homogeneous dense cell with a wax-like dull shine is encountered The nucleus usually lies eccentric A large number of cells contain a number of nuclei Cells even with 10 and more nuclei are observed For the experienced pathologist the very large homogeneous multinucleated cell is different from the foamy lipid cells of xanthomatosis as well as from the Niemann-Pick cells The Gaucher cell does not stain with fat stains like Sudan III and Scarlet R or with Smith Dietrich stain The Niemann-Pick cells, on the other hand, turn dark blue Mallory stain however, colors Gaucher cells strongly blue, while Niemann-Pick cells stain only bluish gray It is important to note that in contrast to xanthomatous tissue and to Niemann Pick cells hemosiderin can always be demonstrated in slides of organs of Gaucher's disease The chemical analysis of the blood does not contribute much to the diagnosis because the pathognomonic substances, the cerebrosides, are not found in the serum in measurable quantities The total lipids cholesterol and the phospholipids are normal or low normal

Differential Diagnosis

The multiplicity of symptoms in Gaucher's disease, splenohepatomegaly, involvement of the osseous system enlargement of the lymph nodes changes in the blood picture and pigmentation simulates so many different clinical syndromes that differential diagnosis is not always easily determined Each of the main symptoms of Gaucher s disease and its relation to other diseases will be discussed separately in the paragraphs which follow

Splenohepatomegaly —The large group of liver diseases with splenic enlargement, Laennec s liver cirrhosis and hematochromatosis may show leukopenia Thrombocytopenia is however, not often associated with this group of diseases The signs of congestion of the portal circulation with or without ascites, which are the outstanding symptoms of this

group are not found in Gaucher's disease The pigmentation in true Laennec's cirrhosis is not patchy In hemochromatosis however the pigmentation of the skin may be similar to that found in some cases of Gaucher's disease The enlargement of the liver with simultaneous signs of portal congestion which in addition to the dysfunction of endocrine glands (pancreas and sex glands) are the outstanding features of hemochromatosis are not found in Gaucher's disease Liver cirrhosis and large firm spleen with leukopenia as well as a tendency to hemorrhages are also characteristic features of Wilson's disease but involvement of the nervous system as well as bulbar and extrapyramidal involvement of the motor nervous system are not found in the adult form of Gaucher's disease

Splenic vein thrombosis (Banti's disease) has many similar features such as a large spleen An enlarged liver is however, rarely found Leukopenia and sometimes thrombocytopenia may be observed with hemorrhages In Banti's disease (splenic vein thrombosis) only the spleen is involved The anemia as well as the thrombocytopenia are early symptoms in contrast to those found in Gaucher's disease Enormous enlargement of the spleen may also be found in chronic malaria and in kala azar Anemia and hemorrhages with intermittent fever are especially characteristic of the latter tropical disease The finding of Leishman Donovan bodies by splenic puncture identifies kala azar In chronic malaria the parasites are found mostly after provocative measures The main point for the differential diagnosis is the fact that there is a complete absence of the involvement of the osseous system in this whole group of infectious and toxic splenohepatomegalies Pain in intervals of the large bones or joints is not present X ray changes significant of the involvement of the osseous system also are not demonstrable Bone marrow puncture in these groups of hepatosplenomegalies will yield normal bone marrow cells

There is however a group of hepatomegalies where the osseous system may also be involved In some cases of malignant lymphogranuloma (Hodgkin's disease) which is called the abdominal or splenomegalic form of Hodgkin's disease pathological changes in the bones may be found These changes rarely involve the large bones In addition they do not demonstrate medullary absorption Expansion and thinning of the cortex or the distal part of the femur also are not observed Biopsy of a lymph node or of the bone marrow reveals the characteristic tissue of malignant lymphogranuloma Syphilitic liver cirrhosis with splenomegaly may be associated with diffuse gummatous bone lesions which

may simulate small or large cysts and expand the cortex of the bones involved The clinical course of syphilitic cirrhosis with bone gummata is entirely different from that of Gaucher's disease The x-ray pictures of the bones, even if there is some localized thinning and expansion of the cortex, always show extensive periosteal lesions These are definitely not found in Gaucher's disease

There is a rare form of neurofibromatosis, von Recklinghausen's disease, which involves skin, bones and in rare instances the liver and spleen The pigmented and pedunculated tumors of the skin and the cafe au lait pigment patches are so characteristic that the differential diagnosis should not be difficult In all these instances bone marrow biopsy is decisive for the diagnosis

Two other lipoidoses, reticular cholesterosis (eosinophilic xanthomatous granuloma) and reticular sphingomyelinosis (Niemann Pick's disease), may occur also with splenohepatomegaly In cases of eosinophilic xanthomatous granuloma the osseous lesions appear in the x-ray films as well defined cyst-like osteolytic lesions The Erlenmeyer flask like shape of the lower end of the femur characteristic of Gaucher's disease is not a feature of eosinophilic xanthomatous granuloma The spleen outstandingly enlarged in Gaucher's disease is not disproportionately enlarged in eosinophilic xanthomatous granuloma However, it is always advisable to confirm the diagnosis by histological and chemical analysis of tissue from a biopsy specimen

Niemann Pick's disease usually does not occur in adults (For a differential diagnosis between Niemann Pick's disease and the acute infantile form of Gaucher's disease, see Differential Diagnosis of Niemann Pick s Disease)

Involvement of the Osseous System—X-ray examination may reveal changes in the osseous system in patients suffering from Gaucher s disease before the spleen becomes enlarged (see case XLIX) In such cases biopsy of the bone lesion is necessary for differential diagnosis

Enlargement of the Lymph Nodes—The peripheral lymph nodes may be enlarged also in the adult form of Gaucher s disease The simultaneously enlarged spleen may suggest some kind of lymphoma especially in cases where complaints hinting to an involvement of the osseous system are not offered by the patient and x-rays, therefore have not been taken In such a case a biopsy of a lymph node should be performed The characteristic nests of Gaucher cells in such a node always will determine the diagnosis These cases which simulate lymphoma are

rare The discrepancy of the enormous spleen and the relatively smaller lymph nodes in these cases clinically indicates the correct diagnosis

Changes in the Blood Picture—The primary blood diseases as the leukemias may also exhibit an enormous spleen The blood findings alone differentiate these leukemias from Gaucher's disease Pathological forms of white cells always are encountered in the blood smear of myelogenous or lymphatic leukemia and in the later stages of aleukemic leukemia In Gaucher s disease on the other hand pathological white cells usually are not found If there is any doubt about the diagnosis bone marrow biopsy will produce definite evidence It should be emphasized again that Gaucher cells cannot be demonstrated in a blood smear

In the later stages of Gaucher s disease the anemia and the tendency to bleeding may be so much in the foreground that the condition may give the impression of some kind of anemia with splenomegaly Myelo sclerosis with splenomegaly due to myeloid metaplasia in the spleen must be considered in the differential diagnosis Bone marrow biopsy is decisive in such cases

The familial tendency in Gaucher s disease is similar to that found also in other anemias such as hemolytic jaundice sickle cell anemia erythroblastic anemia (Cooley s disease) The blood examination immediately differentiates these diseases from Gaucher s disease which exhibits no increased fragility or abnormalities in the shape of the red cells

Bone changes are found also occasionally in erythroblastic anemias The radius and the ulna as well as the skull show osteosclerotic changes in the x ray picture However the characteristic finding in the femur the widening and the thinning of the cortex as well as the cotton wool appearance of the long bones is not found in erythroblastic anemia

The low leucocyte count the thrombocytopenia and the anemia all three of which are prominent in later stages of Gaucher s disease demonstrate that there is an insufficiency of the bone marrow so-called pan myelophthisis (pancytopenia) Mustard gas or urethen is not recom mended in Gaucher s disease because of the danger of pancytopenia Such a condition which is found in different diseases may be due either to the replacement of the bone marrow by other tissue or to an in sufficiency of the bone marrow Bone marrow biopsy reveals the etiology of this type of panmyelophthisis (pancytopenia) It will show that pan cytopenia is due to a replacement of normal bone marrow tissue by Gaucher cells

Abnormal Pigmentation—Diseases with abnormal pigmentation (Ad dison's disease hemochromatosis von Recklinghausen s disease) never

demonstrate dark, brownish, pigmented thickening of the conjunctiva The shape of the pigmented areas is also different from that in Gaucher's disease The pigmentation on the legs is not an early sign of the disease If it is present, it immediately indicates the consideration of Gaucher's disease

Prognosis and Treatment

The prognosis of the chronic adult form of Gaucher's disease depends on the age as well as on the speed at which the symptoms develop It is not very good in cases where the symptoms develop in the first decade of the patient's life The prognosis improves in adolescent cases and may even be called good when the symptoms become manifest in the third or later decades of the patient's life

Tuberculosis of the lungs, which frequently complicates Gaucher's disease, may lead to an early death Progressive anemia which occurs in the later stages of the disease may also terminate the life of the patient

Since reticular cerebrosidosis is a disorder of the intracellular metabolism, treatment, which might alter the intracellular enzymatic balance, is not available It was thought that splenectomy would retard the speed of the disease However, experience shows that the effect of splenectomy is doubtful Cases have even been described where the progress of the disorder increased Splenectomy is advised in cases where the spleen is so large that its volume distends the abdomen As a result the patient is so short of breath that he is hindered in his daily occupation and becomes bedridden In such cases splenectomy is really a relief[13,14,43] (Ottenstein)

Rowland reported that the operative mortality after splenectomy was high, about 20 per cent New statistics on splenectomy are not available However we had no cases of death due to splenectomy in the past six years While influence of splenectomy on the hemorrhagic diathesis and the anemia is marked, it may be only temporary The reduced number of thrombocytes increases to normal after splenectomy Sometimes even values higher than normal are observed The leucocyte count after splenectomy frequently is elevated also but later remains at a normal level In most cases the anemia returns to its original state a short time after the patient has recovered Transfusions may give symptomatic relief in later stages of the disease Iron and arsenicals have only symptomatic effects

X ray treatment may result in a transient decrease in the size of the spleen in early stages of the disease However in cases where the disease is of long duration and the spleen is enlarged considerably, x ray therapy usually is not effective X ray therapy of the long bones is most helpful in cases with excruciating pains of the extremities The pain disappears after the radiation X ray treatment must be repeated in each attack of bone and joint pain This treatment should not be applied as a prophylaxis for the osseous involvement but only as a measure to allay pain The pain may be of such severity that morphine is required

In all instances where x ray therapy is applied, the number of leucocytes must be watched carefully so that they do not drop below 3 000 This treatment should not be undertaken if the leucocyte number is below this count Transfusions should be given in cases where there is severe anemia and bleeding

B GENERALIZED (ACUTE) INFANTILE FORM OF GAUCHER'S DISEASE

Clinical Course

One year after Pick in his classical paper had separated Niemann Pick's disease from Gaucher's disease Oberling and Woringer[96] reported outstanding differences between the manifestations of Gaucher's disease as they occurred in infancy on the one hand and in children and adults on the other hand While the clinical picture as well as the clinical course is distinctly different in both groups, the underlying cause of both conditions is the same that is reticular cerebrosidosis

Oberling and Woringer[96], who observed four infants out of a family of five children found that they showed a marked neurological syndrome in addition to the splenohepatomegaly The following symptoms were observed, rigidity of the neck opisthotonus, increased muscular tone a tendency to maintain the arms in certain positions for long periods of time laryngeal spasms dysphagia trismus and strabismus There was also a marked progressive loss of sensation and a complete lack of interest in the environment

Meyer[83 84] who collected similar cases from the literature also added one of his own He discussed the neurological picture as a pseudobulbar syndrome Hoffman and Makler[61] reported the first case in this country of an infant with Gaucher's disease and neurological symptoms Aballi

demonstrate dark, brownish, pigmented thickening of the conjunctiva. The shape of the pigmented areas is also different from that in Gaucher's disease. The pigmentation on the legs is not an early sign of the disease. If it is present, it immediately indicates the consideration of Gaucher's disease.

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Since reticular cerebrosidosis is a disorder of the intracellular metabolism, treatment, which might alter the intracellular enzymatic balance is not available. It was thought that splenectomy would retard the speed of the disease. However, experience shows that the effect of splenectomy is doubtful. Cases have even been described where the progress of the disorder increased. Splenectomy is advised in cases where the spleen is so large that its volume distends the abdomen. As a result the patient is so short of breath that he is hindered in his daily occupation and becomes bedridden. In such cases splenectomy is really a relief[13, 14, 43] (Ottenstein).

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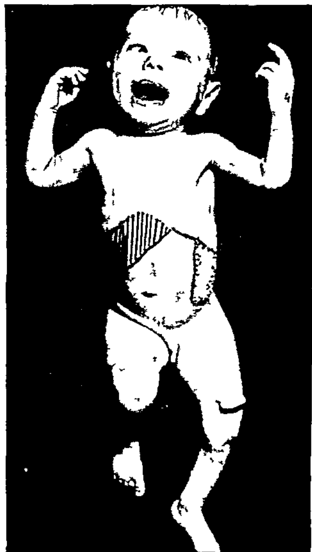


Fig 1 4 Acute infantile form of Gaucher s disease Note strabismus opisthotonus and increased muscular tone (Form Aballi and Kato (Case L))

difficult breathing not associated with the intake of food She was brought to another hospital because of a cold difficulty in feeding and constipation She had marked stabismus and opisthotonus At this time a palpable spleen

and Kato[1], who collected 17 cases from the literature, reported one case of an infant with such a neurological syndrome These authors stated that in addition to these cases there were 10 cases of infants reported in the literature in which the onset of the disease had taken place during the first year of the child s life, but in which neurological manifestations were totally absent With one exception the infants in the last group were past six months of age, when the first symptoms appeared, in contrast to the group which displayed neurological symptoms in which the onset of the disease occurred in the first half year of the infant's life In both groups however, the course was rapid with fatal termination It is remarkable that the neurological syndrome develops only in the first seven months and that the infants are born healthy The psychic changes as well as the neurological signs develop progressively in a child apparently healthy at birth Similar observations have been made in children where the diagnosis Niemann-Pick's disease is made

Since Aballi and Kato's review of the literature cases of generalized infantile Gaucher's disease have been reported by the following authors de Lange[7, 8], Stransky and Peeache[130b] Tosco[131b], Schairer[1 1 1 1b], Frisell[14] Garrahan Gambirasse Albores and Moran[51b], Franco[49b] and Robb Smith and co workers[118] The organs of the two brothers observed by Robb-Smith were analyzed by Ottenstein, Schmidt and Thannhauser[9]

Clinical Case

The case report of Aballi and Kato (Fig 114) may be quoted because the observations are identical with the 17 other cases of the literature abstracted in their paper

Case L—C R appeared normal at birth with low forceps delivery weighing 3 015 grams and was 50 centimeters in length The child s parents were American-born and non Jewish They were in good health and there was no family history of any significance There were no other children and no miscarriages

The baby did well and upon her dismissal from the hospital weighed 3 450 grams Shortly after she was taken home the parents noticed that she tended to keep her neck retracted and had a slight squint The child was breast fed and continued to gain weight up to the age of two months At that time she weighed 5 000 grams

Towards the early part of the third month after she had been weaned she began to take feedings poorly At times she choked and had attacks with

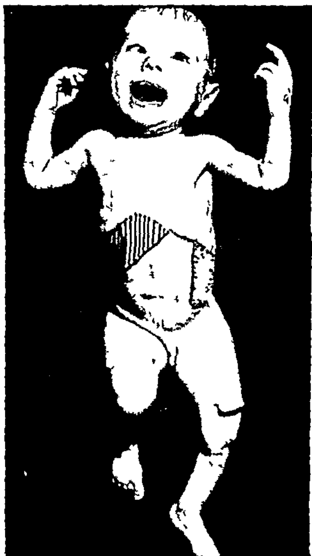


FIG 114 Acute infantile form of Gaucher s disease Note strabismus opisthotonus and increa ed mu cular tone (Form Aballi and Kato (Case L))

difficult breathing not associated with the intal e of food She was brought to another hospital because of a cold difficulty in feeding and constipation She had marked stabismus and opisthotonus At this time a palpable spleen

was observed, but no neurological manifestations were noted The child weighed 4 300 grams Blood examination revealed 40% hemoglobin 5 300 white cells 19% neutrophiles, 72% lymphocytes 7% monocytes and % eosinophiles Urine was negative In the following weeks the opisthotonus and strabismus were intensified The spleen grew in size, and the liver was palpable two fingers below the costal margin The child was readmitted to the hospital

The physical findings showed a four-months old undernourished infant who weighed 3 900 grams The head was retracted and the back arched in opisthotonus The neck could not be bent forward without difficulty The arms were elevated to the level of the shoulders with flexion at the elbows and adduction so that the hands fell into position over the lower part of the face The legs were in a position of flexion The infant tended to maintain these positions for a long period of time She did not appear acutely ill The skin was pale, but there was no pigmentation or rash The ears were negative The eyes showed convergent strabismus with fine nystagmus The pupils reacted to light, and the fundi were normal The child appeared to perceive light but did not follow objects with her eyes Although there was no facial asymmetry, her expression was peculiar The cervical lymph nodes were moderately enlarged The lungs were clear The heart was normal The abdomen was not distended The liver was enlarged two fingers breadth below the costal margin The spleen reached down to about one centimeter above the left iliac crest (Fig 114) There was a reducible protrusion of the umbilicus The genitals were normal The tendon reflexes were brisk but not increased There was no clonus Oppenheim signs were positive The abdominal reflexes could not be elicited The extremities showed definitely increased muscular tone

Blood count showed 65% hemoglobin 4 850 000 red cells 11 600 white cells 46% neutrophiles 3% monocytes 4% eosinophiles and 1% basophiles There were no nucleated red cells in the peripheral blood stream The Wassermann reaction was negative The spinal fluid was clear The x rays of the bones revealed no abnormalities

While in the hospital the child was unable to swallow food properly She took no more than 2 5 oz of the formula at one feeding A week later dullness was noted over the right lower lung X ray revealed pneumonic infiltration extending outward and developing from the right hilus Temperature was 10- - F During the periods of febrile attacks the child had occasional spells of transient cyanosis A sternal marrow puncture was performed and the smear showed characteristic Gaucher cells Total cholesterol was found to be 1-9 mgm per cent

The patient was taken home upon the request of the parents but was brought back two days later because of laryngeal spasms She was extremely restless, cyanotic and pale Daily hypodermoclysis and repeated intravenous

administration of fluid improved her condition considerably Blood count showed 59/ hemoglobin 4 800 000 red cells 5 600 leukocytes 6/ neutrophiles 66/ lymphocytes / monocytes 1/ easinophiles and 1/ basophiles On the seventh day of her hospital stay the patient again had a temperature of 104 F and diarrhea The child suddenly became cyanotic and respiration stopped abruptly The child s age now was five months

The following findings were revealed by autopsy (1) lipoid histiocytosis Gaucher type with extreme splenomegaly and moderate enlargement of the liver (2) lipoid storage in the lungs lymph nodes thymus bone marrow and lymphoid tissue of the intestines (3) acute bronchopneumonia (4) hemorrhages in the serous membranes According to the chemical analysis the liver and spleen contained cerebrosides

In most cases the parents first perceive a lack of gaiety and vivacity in the infant These signs are followed by retarded physical and intellectual development The child becomes thin Its abdomen enlarges and on palpation one finds an enlarged spleen Subsequently the liver also enlarges Opisthotonos develops The head is thrown back The arms which are elevated to shoulder level, are flexed at the elbows and held more or less tightly to the body The legs also are fixed and rigid The spasmodic rigidity makes movement difficult and the infant becomes stiff as a wooden figure (Oberling and Woringer[96]) Dysphagia as well as trismus early make the child unable to take regular feedings Laryngeal spasms accompanied by cries and spells of cyanosis occur frequently The infant neither sees nor hears He becomes increasingly mentally debilitated until fever develops mostly with signs of pulmonary involvement The infant dies during a spell of cyanosis The tendon reflexes are exaggerated Sometimes Babinski and Oppenheim signs are present Chovstek and Trousseau signs are absent Progressive and rapid cachexia accompany the striking neuromuscular syndrome Pinguecula like brownish deposits on the conjunctiva as well as pigmentation of the skin or mucous membranes has not been reported The cherry colored spot in the macula of the retina has not been found in any case so far described The duration of the affection is about two to six months The infant succumbs at the end of the first or second year as a result of extreme cachexia

Morbid Anatomy

Necropsy in all these infantile cases reveals that the organs involved are not restricted to the liver spleen bone marrow and lymph nodes

as it is in adult cases with Gaucher's disease Nests of cells which contain lipid material, are found also in thymus, lungs, adrenals and the lymphoid tissue of the intestines The findings in the central nervous system, as pointed out by Jenny[73] as well as by Oberling and Woringer[76], are unique Typical Gaucher cells are not found in the brain tissue The pathology is restricted to the large and small pyramidal cells of the cerebral cortex Although the lesions are the most extensive in the occipital and parietal regions, they are found also throughout the cortical substance The pyramidal cells are sharp in outline with ordinary stains The ganglion cells are so retracted that they appear condensed or "mummified" Their contours are irregular Many of these cells contain vacuoles of variable sizes some of which are large enough to distend the cell bodies The organs of two infant brothers were histologically studied by Robb-Smith and co-workers (For chemical analysis of these organs, see Tables XL and XLI)

Chemical Analysis of Organs

Aballi and Kato[1] reported the chemical analyses of liver and spleen of their case (Table XXXIX)

TABLE XXXIX

	Liver	*Spleen*
Weight of sample	81 0 gm	7- 0 gm
Weight of lipoidal extract	4 57 gm	4 84 gm
Weight of extract dry residue	1- gm	9 4 gm
Total solids	16 6 gm	14 2 gm

Percentage of total lipids of the total lipoidal extract

	Liver	*Spleen*
Free cholesterol	4 5	5 6
Cholesterol ester	1 2	1 6
Phosphatides as lecithin	44 9	30 9
Kerasin	43 9	36 6
Balance neutral fat plus fatty acids	5 8	25 6

If these figures which indicate the percentage of total lipid extracts of the cholesterols phospatides and kerasin are converted into figures which give the percentage in dry organs (total solids), the results are

similar in regard to the spleen to those obtained by the author and co-workers in the case of a seven year old boy

	Liver	Normal	Spleen	Normal
Total cholesterol	1 6 mgm	1 0 mgm %	2 30 mgm /	0 87 mgm
Total phosphatides	1 3	0 8	10 4	8 56
Cerebrosides	1 3	traces	1 47	traces

Chemical Analysis of the Organs of Two Siblings Observed by Robb Smith and Co-workers (Pathological Department of the Radcliffe Infirmary, Oxford, England)

The analyses (see Tables XL and XLI) were carried out by Otto Schmidt and Thannhauser with a method which made the estimation of galactosidocerebrosides as well as glucosidocerebrosides possible

TABLE XL

Organs	Dry Weight of Sample of Organ	Galactosido-cerebrosides	Glucosido-cerebro-sides	Galactosido-cerebrosides in normal adult human organs
Brain	300 mgm	2.6	Traces	4.0-6.0 (1.0)
Spleen	90	3 (3.0 /)		0 /
Liver	237	3 /	"	0 16 /
Lungs	160	6 8 /		0.6 /
Heart	186	2 3 /	"	0 4
Bone marrow	466	1 3 /	"	—
Kidney	188	3 1 /		0 /
Intestine I	26	3 2 /	"	—
Intestine II	209	8 /		—
Pancreas	2 3	3 1 /	"	—

Cerebrosides in the brain of a one-day old child

These analyses demonstrated the remarkable fact that the kind of cerebrosides present in the organs of each sibling was different The organs of the younger infant contained only galactosidocerebrosides those of the other brother showed both galactosido as well a glucosido cerebrosides the latter predominating These most interesting findings can only be recorded with no explanation however yet available These figures moreover are in accord with our findings on spleens in

three different adult cases of Gaucher's disease, which revealed that, while glucosidocerebrosides prevail, an increase of galactosidocerebrosides may also occur

The analyses of different organs in infantile Gaucher's disease demonstrated in all organs tested with the exception of brain an accumulation of cerebrosides, i e an involvement of all organs in the infantile form In this respect a parallel with Niemann-Pick's disease is justified where an increase in the lipid characteristic of the disease occurs in all organs but the brain Despite the fact that the brain is diseased in both diseases the pathognomonic lipids of each syndrome are not increased in either condition as is revealed by chemical analysis

TABLE XLI

Organ	Dry Weight of Sample	Galactosido-cerebrosides mgm / Dry Weight	Glucosido-cerebrosides mgm / Dry Weight	Ratio Galactosido cerebrosides to Gluco-cerebrosides	Total Cerebrosides mgm / Dry Weight	Galactosido cerebrosides in normal human organs mgm / Dry Weight
Spleen	1 8 gm /	0.44 mgm	0.95 mgm	1.0 2 1	1.44 mgm /	0 1 -0 5 mgm
Liver	1 77	0 28	0.05	5.6 1	0 33	0.05-0 15
Brain	0 66	3 25	0 "	0	3 25	4.0 -6.0 "
Lung	1 17	0 61	0.43	1.4 1	1.04	0 1 -0 6 "
Kidney	1 7	0 29	0 25	1 1	0 54	0 1 -0 7
Pancreas	1 83	0.09	0.05	1 8 1	0 14	0 1 -0 3
Thymus	1.94	0 30	0 30	1.0 1	0 60	— —
Suprarenal	0.88	0 0	0 99	2 1	0 29	— —

Cerebrosides in the brain of a one day old child mgm /

Differential Diagnosis

The involvement of lungs, adrenals the intestines and the presence of cerebral symptoms as well as the rapid and deadly course of the acute infantile form of Gaucher s disease is very similar to the clinical manifestations of Niemann-Pick's disease The features are in many respects identical Niemann Pick's disease has the same insidious onset in the first six months of the infant's life and the same fatal ending in the second year It has similar symptoms of the nervous system and also shows complete mental deterioration It is probable that, of the twenty-seven cases

reported as cases of acute infantile form of Gaucher s disease some were Niemann Picl s disease Chemical analysis of the organs should determine conclusively the differential diagnosis between the acute infantile form of Gaucher s disease and Niemann Pick s disease Chemical analysis with determination of cerebrosides was carried out only in Abilli and Kato s[1] and in Robb Smith s[118] cases In the future the diagnosis of the infantile form of Gaucher s disease can only be accepted after biopsy and chemical analysis of the organ The quickest and easiest way to decide is by carrying out a total phospholipid determination which is possible on a wider scale with a little piece of bone marrow or lymph node tissue after drying and extracting it carefully with chloroform-methanol Very high total phospholipids (500 1000 mgm per cent) are found in Niemann Pick's disease while in Gaucher s disease the total phospholipids are normal (150 to 50 mgm per cent) The method of sphingomyelin determination of Schmidt Benotti Hirschman and Thannhauser[1] and the method of cerebroside estimation of Ottenstein Schmidt and Thannhauser[97] make it possible to determine sphingomyelin and total phospholipids as well as cerebrosides in small pieces of tissue

The differential diagnosis of both infantile diseases on the basis of the clinical symptoms as well as on the microscopic differentiation of the Gaucher and Niemann Picl cell may be ambiguous The clinical symptoms which may help distinguish the infantile form of Gaucher s disease and Niemann Picl s disease are given in the following tabulation (Table XLII)

TABLE XLII

Symptoms	Acute infantile form of Gaucher s disease	Niemann Pick s disease
Pigmentation	No pigmentation	Brownish pigmentation on the exposed parts and mucous membranes often present
Neurological signs	Pseudobulbar syndrome Hypertonic laryngeal spasms Flexed arms and elbows Strabismus	Usually flabbiness of the muscles and hypotonia Not present
Fundi	Negative	Cherry red spot at macula lutea
Blood	No Gaucher cells Leukopenia	Large Niemann Pick cells No leukopenia
Total cholesterol in serum	Normal or low normal	High normal or increased

Differential diagnosis of acute infantile Gaucher and Niemann Pick diseases may be possible by histological examination of bone marrow or lymph node tissue obtained by biopsy (Table XLIII)

TABLE XLIII

	Acute infantile Gaucher's disease	Niemann Pick's disease
Unstained cell	Homogeneous dense wax like	Little droplets in the cell
Nucleus	Eccentric and many	Rarely more than three
Size of cell	Average 80 micra	Average 40 micra
Sudan III	Negative	Positive
Smith Dietrich stain	Slightly colored	Deep dark black blue
Mallory stain	Strongly blue	Bluish gray

While in adult cases the changes in the osseous system revealed by x-ray are the leading symptoms for the diagnosis of Gaucher's disease osseous pathology in the acute infantile form revealed by x ray has not yet been reported The neurological pseudobulbar syndrome is very helpful for the diagnosis of infantile Gaucher's disease However, as it is not present in infantile cases which did not start before the first six months it is not pathognomonic of the acute infantile form Expert staining or, more preferably, chemical analysis of material from biopsy is necessary for a conclusive diagnosis of the infantile form of Gaucher's disease

Prognosis and Treatment

The acute infantile form is fatal within a few months after the first signs of the disease become evident, the average duration is six months The involvement of the brain with ensuing cachexia is the cause of the rapid progression and of the early death This rapid course is in contrast to that in adults in which the disease has a chronic course with a relatively good prognosis In infantile Gaucher's disease no therapeutic measures are of value

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PART V

NIEMANN-PICK'S DISEASE

(RETICULAR AND HISTIOCYTIC SPHINGOMYELINOSIS)

Definition

Synonyms—Lipoid cell splenohepatomegaly Niemann Pick type lipoid histiocytosis essential lipoid histiocytosis phosphatide lipoidosis

Definition—Niemann Pick's disease is a rare congenital familial constitutional disorder of cellular metabolism of reticular and histiocytic cells The histiocytes and reticulocytes of all organs may be involved in the disease in contrast to Gaucher's disease where only the lymph hemopoietic system liver spleen lymph nodes and bone marrow are essentially affected

Niemann Pick's disease is characterized by an accumulation and retention of the diaminophosphatide, sphingomyelin within reticular cells and histiocytic cells in the end phases however involving epithelial cells and cells of mesenchymal origin A slight increase in cholesterol and cholesterol esters may be found in the serum as well as within the cell The monoaminophosphatides lecithin and cephalin are not involved in the disease The glia cells of the brain demonstrate characteristic anatomical changes but no accumulation of sphingomyelin

The following clinical symptoms are characteristic of Niemann Pick's disease enlargement of liver spleen lymph nodes diffuse pigmentation of the skin and patchy bluish black spots of the mucous membrane of the mouth digestive disturbances physical and mental deterioration slight hypotonicity and emaciation of the extremities, mongoloid facial expression extreme cachexia and rapid progression resulting in the death of the patient in the first two years of life Hyperlipemia of a slight grade may become apparent in the course of the disease

Historical Note

In 1914 Albert Niemann who was killed in the World War I published the first observation of an affection in an infant of seventeen months which was similar to Gaucher's disease but showed diffuse dis

tribution of the large pale cells in all organs He described it as 'ein unbekanntes Krankheitsbild' Two years later Knox, Wahl and Schmeisser[40] reported two similar cases occurring in sisters One sister was reported as having Tay-Sachs' amaurotic idiocy with characteristic red spots in the macula In 1921 Siegmund[63] reported a case of an infant nine months old, which he believed to be a very early stage of Gaucher's disease Mandlebaum and Downey[44] doubted whether these cases should be classified as Gaucher's disease These authors clearly demonstrated the clinical and pathological differences between the two conditions

However, credit must be given to Ludwig Pick[48], who perceived that this condition which was distinctly different from Gaucher's disease, was a new pathological and clinical entity This condition is now called Niemann-Pick's disease in the literature Pick demonstrated the special anatomical features of this disease on the histological material of Niemann[46] and Siegmund[63] as well as that obtained from a case of his own

Bloom and Kern[11] made the first chemical analysis of the liver and spleen in a case of Niemann Pick's disease In contrast to Gaucher's disease they found an increased content of phospholipids in these organs These authors agreed to the opinion of Ludwig Pick and proposed the name 'lipoid histiocytosis' for the disease

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Dusendschon[17b] described two brothers 29 and 33 years old This is the first time that Niemann Pick s disease has been observed as a chronic disease patients of adults age Dusendschon[17b] confirmed the diagnosis of Niemann Pick s disease in these adults by chemical analysis of the organs (Pfandler s[4] patients are the same as those described by Dusendshon)

Histology and Morbid Anatomy

The striking features macroscopically revealed at autopsy are involvement of the liver and spleen (Fig 115) generalized enlargement of the lymph nodes and involvement of the lungs and bone marrow Microscopically there is no organ where Niemann Pick cells are not found They are present in the esophagus and stomach and in all parts of the intestines Niemann Pick cells are found in the mucosa and submucosa especially in the deeper layers of the mucous membranes The ganglion cell of the plexus mesentericus as well as the intramural nerve plexus of the mucosa are interspersed also with Niemann Pick cells Nests of these cells are especially demonstrable in the lymphoid apparatus of the intestines The muscle fibers of the heart and skeletal muscles do not show destruction However Niemann Pick cells are demonstrable with Smith-Dietrich staining in the surroundings of the muscle fibers and in the near vicinity of smaller vessels Large foam cells are intermingled in the cardiac and muscular nerves They are found also in the area of the pulpae of the teeth especially around the blood capillaries and nerve fibers All endocrine organs prostate testis thyroid pancreas and especially thymus and adrenals show dark precipitates and Niemann Pick cells with Smith Dietrich staining Foam cells are found conglomerated in groups in the connective tissue of the wall of the gall bladder and urinary bladder Niemann Pick cells are found in the nerve sheaths especially in the perineurium The skin is practically the only organ where Niemann Pick cells have not been demonstrated The vicinity of blood vessels in the skin also does not show very many foam cells The brain does not show typical Niemann Pick cells, however

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all the organs in which they are present, are replaced by or transformed into Niemann Pick cells There are only very rare cases where Niemann Pick's disease is not "maximally" developed and only some of the organs are involved In Gaucher's disease on the other hand only the lymph hemopoietic apparatus which consists of the spleen liver, bone marrow and lymph nodes, are affected.

The foamy Niemann Pick cells are not a part of a granulomatous or inflammatory tissue like the foam cells in the different types of xanthomatous disease Eosinophilic xanthomatous granuloma in its first phase of development shows intensive reticulo histiocytic proliferation In the later phases cholesterol accumulates in some of the reticulum cells and histiocytes thus gradually developing into foam cells In Niemann Pick's disease however the foamy Niemann Pick cells originate at the beginning of the disorder and are not replaced subsequently by fibrous tissue Neither do they deteriorate like the foam cells in the hypercholesteremic type of xanthomatosis where the xanthomatous tissue may often in some areas and a milky fluid containing cholesterol crystals exudes It is doubtful whether there is any dissolution of Niemann Pick cells in the organs involved in Niemann Pick's disease

The spleen is always greatly enlarged The smallest weight on record is 6 gms (Bloom[8]) and the largest 480 gms (Kramer[4]) The consistency of the spleen usually is quite firm The color is a peculiar salmon pink, and on section a slight yellow mottling with grayish areas is visible The malpighian bodies, which are widely separated and usually surrounded by a thin red zone stand out prominently The liver which may either be soft or firm in consistency is greatly hypertrophied Its color is whitish yellow In gross appearance it closely resembles a fatty liver such as that found in phosphorus poisoning The spleen and liver which may together extend to the iliac crest almost completely fill out the abdominal cavity (Fig 115) In contrast to Gaucher's disease where the spleen usually is much larger than the liver the two organs are equally enlarged in Niemann Pick's disease 'The superficial lymph nodes may or may not be enlarged Those of the abdominal cavity are always somewhat larger than normal especially around the abdominal organs, pancreas spleen and liver The color of the lymph nodes is also slightly yellow with a gray tint The lungs show a bright yellow mottling particularly beneath the pleura and extending into the septa All the organs may have a slightly greasy and shiny surface and on section exude a yellowish brown material (Rowland[3]) The fluid which may be artificially expressed from the involved organs, is milky in the last

there are characteristic changes of the ganglion cells, which seem to be distended and inflated like small balloons (Fig 118)

There is a striking difference between Niemann-Pick's and Gaucher's disease In the first disease the reticular cells and histiocytes, in almost

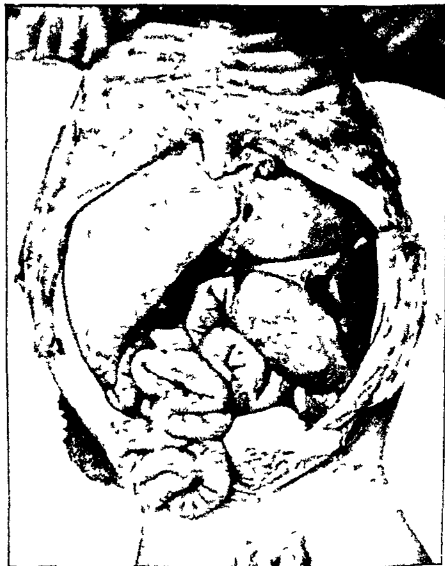


Fig 115 Niemann Pick's disease Gross anatomy of the abdomen Note the large fatty liver and greatly enlarged spleen Compare with Gaucher's disease where only the enlarged spleen fills out the abdomen Through the courtesy of Dr Sidney Farber Pathological Department of the Children's Hospital Boston

The changes consist not only of cell transformation of the reticular cells and histiocytes but also of a vacuolation of the parenchymal cells In the liver the epithelium of the gland becomes so highly vacuolated that it is difficult to separate the parenchymal cells from the foam cells The same change may occur also in other organs like thyroid thymus pancreas testicles and kidneys Lipid droplets accumulate in the anterior lobe of the hypophysis and in the glia cells of the posterior lobe as well

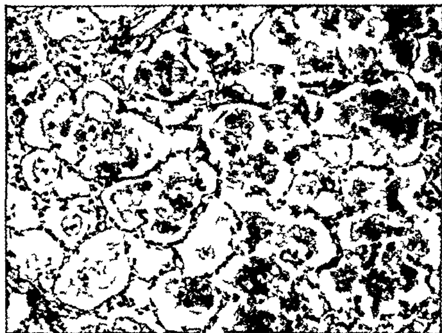


Fig 116 Lung in Niemann Pick's disease Note that the alveoli are filled out with masses of Niemann Pick cells Through the courtesy of Dr Sidney Farber Pathological Department of the Children's Hospital Boston

as in the tracheal and bronchial epithelium the mucosa of the fallopian tubes and the uterus They are found by special staining in the cartilage and in the sheaths of the medullated nerves (Pick[18, 19] Bloom[19])

Scheidegger[6] who made a very remarkable *histological study* of the brain of Baumann's case[6] compared the histological findings with those of infantile amaurotic idiocy He stated that the histological pictures of infantile amaurotic idiocy and Niemann Pick's disease are identical although there are differences in regard to the areas of the brain involved

phases of the disease The serum may also have a slight milky appearance

The other organs in the body may be yellowish in color but are mostly without gross change The suprarenals occasionally are enlarged One case with calcified adrenals is reported The brain sometimes is quite firm and has a waxy appearance The subcutaneous fat in the final stage of the disease is greatly reduced

Histology —Microscopically, the spleen, liver and lymph nodes and most of the other organs demonstrate an accumulation of large, pale cells foam cells, Niemann-Pick cells, which have almost entirely replaced the parenchyma of these organs Most of the glandular organs, although not appreciably enlarged, are flooded also with these large cells

"The spleen is almost completely transformed into a conglomeration of foam cells, which replace the pulp between the sinuses The cells lining the sinuses usually are not vacuolated Scattered through the pulp *between the foam cells are a few large and small lymphocytes* The malpighian bodies usually are widely separated from each other by great masses of foam cells Very large foam cells appear in the germinal centers where the development of these cells from embryonic reticulum is readily demonstrable The foam cells in the liver are somewhat smaller than those in the spleen and the vacuoles vary more in size The foam cells completely fill the sinusoids and the liver structure is hardly recognizable In the late stage of the disease there is a slight increase in periportal connective tissue, but it is much less than that found in the late stages of Gaucher's disease There are only the two cases of Dusendschon[1 6] and Pfandler[4] of chronic Niemann-Pick s disease in adults on record where definite cirrhotic changes developed in the liver

The lymph nodes are filled with nests of foam cells entirely similar to those found in the spleen Here, too, the cells may originate in the embryonic reticulum cells The bone marrow contains many foam cells, but they are not so numerous as those found in the spleen Great numbers of foam cells are found in the septa and alveolar spaces of the lungs (Figs 116 and 117) The small alveoli and many of the air spaces are filled with these large cells *which look like twisted bands* The foam cells in the suprarenals are localized between the cortex and medulla and appear to thicken the latter greatly The thymus presents the same picture The lymphoid tissue of the gastrointestinal tract, in fact the connective tissue and reticulum running through all the glandular organs as well as that in the skin, shows the same interspersement with large foamy cells" (Rowland[3])

two different clinical entities Their opinion conforms with the one expressed in the first edition of this section based on our chemical analyses of visceral organs of both disorders In Niemann Pick s disease all visceral organs show Niemann Pick cells with enormous accumulation of sphingomyelin On the other hand in Tay Sachs disease the sphingomyelin content of the visceral organs is normal

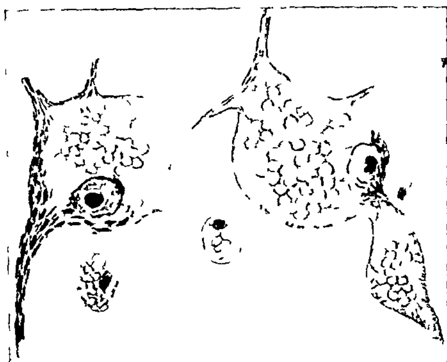


Fig 118 Two ganglion cells from the cortex Note the balloon like inflation of the body of the cell and the tigroid bodies (Reproduced from S Scheidegger in Baumann T Ergebn d. allg Path u path Anat., 1936 XXX 287)

The sphingomyelin content of the brain and cerebellum in these two disorders is normal The characteristic changes of the ganglion cells of the brain in these syndromes is not due to an accumulation of sphingomyelin within these cells As Schaffer[8, 9] pointed out a degenerative process probably occurs in the ganglion cells which is common to a group of heredofamilial diseases of the central nervous system

In both diseases the ganglion cells of the brain show enormously blown up cells and disintegration of the tigroid bodies (Fig 118) There are also changes of the fibrils with complete disappearance of the intercellular net of fibrils The ganglion cells and the glia cells stain dull brick red with Sudan III This shade is entirely different from that of the shiny, yellowish red bodies in the granulated fat cells and in vascular endothelial cells These cell enclosures stain strongly with Weigert stain All areas of

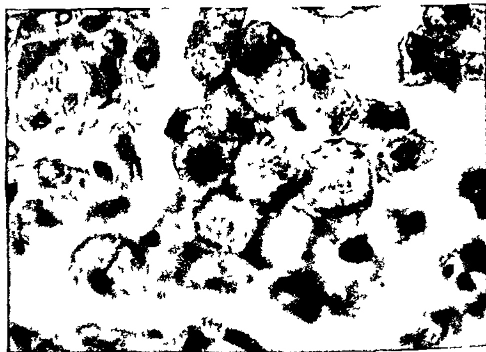


Fig 117 High magnification of Niemann Pick cells and alveolar cell in the lumen of an alveolus of the lung Through the courtesy of Dr Sidney Farber Pathological Department of the Children s Hospital Boston

the brain demonstrate the same degenerative process of the cells (Fig 119) Some areas are only slightly involved while other areas like the fossa calcarina are severely affected The cerebellum is the most involved area of the whole central nervous system In this organ there is gliosis with an exuberant growth of Bergman's fibers Almost all Purkinje cells in the cerebellum are destroyed

Rothstein and Welt in an excellent histological study of infantile amaurotic idiocy and its relation to Niemann-Pick s disease conclude that both diseases despite the histological similarity of the bone lesions are

from those found in amaurotic idiocy, Tay Sachs type While the ganglion cells are damaged they are present in normal numbers In Tay Sachs disease descending degeneration of the neurones and reduction of the layer of the nerve fibers are found in addition to optic atrophy Neither of these two characteristics of Tay Sachs disease was found in the Niemann Pick case, which was examined very carefully by Rintelen Earlier descriptions by Goldstein and Wexler[3] also did not show complete opticus atrophy but only the beginning of degeneration and infiltration of the connective tissue with questionable foam cells

Rintelen[5] believes that the amaurosis in Niemann Pick's disease is not the result of a peripheral opticus atrophy but is due to severe changes in the area of the visual cortex The damage of the retina is caused by degeneration of the ganglion cells which show fine fat and fat like granules in the swollen cell protoplasm There is no reduction in number of ganglion cells There is an increase of glia elements partly filled with fat in the inner layer of the retina The changes in the fovea centralis are due first to an edematous swelling of the inner reticular zone around the macula secondarily to lipid infiltration of the ganglion cells around the macula and third to increase of glia cells which reduce the transparency The appearance of the cherry red spot should be due to the contrast of a normal fovea in the midst of a less transparent and damaged area around it According to Rintelen this red spot is not typical of Tay Sachs or Niemann Pick's disease but is due to a decreased transparency around the undamaged fovea It may occur in any disease where the area around the fovea has a reduced transparency It must however be emphasized that this condition is according to the author's knowledge found only in Tay Sachs amaurotic idiocy and in Niemann Pick's disease

Origin and Nature of Niemann Pick Cells

The Niemann Pick foam cell is a large pale ovoid or round cell varying in diameter from twenty to forty five or more microns (Fig 120) It is not found associated with granulomatous tissue as is the foam cell in eosinophilic xanthomatous granuloma (essential xanthomatosis of the normocholesteremic type, lipid granuloma Schuller Christian disease) Inflammatory reactions around the Niemann Pick cells usually are not demonstrable The Niemann Pick cell contains abundant cytoplasm which in its fresh stage is loaded with coarse bright granules

Klenk[31, 32, 33] found that a peculiar glucoside, which he called gangliosides is increased in the brain of Niemann-Pick's disease to 1 5 mgm per cent (0 3 mgm per cent normal) and in Tay-Sachs' disease to 4 to 8 mgm per cent It still remains to be seen whether the increase of gangliosides is specific for brain in Tay-Sachs' disease, or whether this substance may be present also in greater quantities in the brain of other heredofamilial disorders of the central nervous system

Oppikofer[4] described changes in the ear in Niemann Pick's disease In contrast to Gaucher's disease where the Gaucher cells are found in the bone marrow of the corpus petrosum, the Niemann Pick cells are

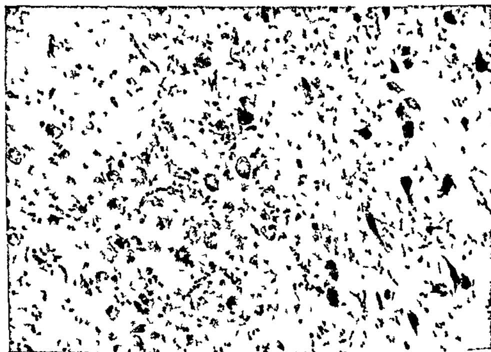


FIG 119 Corpus quadrigeminum Note the bloated gaglion cells (Reproduced from S Scheidegger in Baumann T Ergebn d allg Path u path Anat 1936 XXX 288)

found not only within the bone marrow but also in other places of the middle and inner ear They are present in the exudate of the epitimpanum in the macula atriculi and in the vicinity of the ganglion gasseri

The first studies of the histological changes of the retina were made by Goldstein and Wexler[28] Newer data were presented by Rintelen on the Baumann case He concluded that the fundi changes are different

from the homogeneous Gaucher cell However the distribution in the tissue as well as the cellular proliferation of the surrounding tissue is entirely different so that the histological differential diagnosis is apparent

Concerning the histogenesis of the Niemann Pick cell the opinion in the literature is not uniform Pick himself made the following statement *The histogenesis of the storage cells in Niemann Pick s disease is much* too universal to permit acceptance of the designation lipoid histiocytosis Since in Niemann Pick s disease cells of all the body tissues are involved it appears really necessary to explain the disease upon a single composite basis and not for example to limit it to a primary insufficiency of the reticulo endothelial apparatus

Bloom[10] in a very extensive and sound study of the histogenesis of essential lipoid histiocytosis (Niemann Pick s disease) expressed the following opinion In studying the tissues for the source of the lipoid-laden phagocytes certain genetic relationships between some of the various connective tissue cells of the human organism become apparent All of the stages in the mobilization of the embryonic mesenchymal cells (Maximow) and the mature histiocytes as well into large lipoid containing histiocytes can be seen with great clarity The foam cells develop from the resting endothelial and Kupffer cells in the liver from the reticulum cells of the lymph nodes the reticulum cells (exclusive of the littoral cells) in the spleen and bone marrow from the reticulum cells of the medulla of the suprarental gland from the septum cells of the lung from the resting wandering cells of the connective tissue and the perivascular embryonic cells and phagocytes all over the body The intervascular agranulocytes also develop into lipoid filled macrophages (foam cells) in the lung and the kidney The author agrees with Bloom s observation and theory concerning the histogenesis of the Niemann Pick cells

There is no doubt that in Niemann Pick s disease the development of Niemann Pick cells foam cells is not restricted to the reticulum cells of the lymphohemopoietic apparatus as it is in Gaucher s disease of the chronic adult form In the infantile acute form of Gaucher s disease however the development of Gaucher cells is not found in the reticulum cells of liver lymph nodes and bone marrow alone These cells rather spread all over the body where reticulum cells and histiocytes otherwise are found The infantile acute form of Gaucher s disease and Niemann Pick s disease exhibit marked similarity in regard to the organs involved The clinical features are therefore also similar The fact that the macrophage system reticulum cells and histiocytes are more widespread

When it is treated with ordinary fixing reagents that dissolve the fat, it becomes a fine areolar network giving a foamy, vacuolated appearance from which the name, "foam cell", Schaumzelle, was derived In contrast to the Gaucher cell, which is not foamy or vacuolated but opaque and homogeneous, the Niemann-Pick cell has only one or two nuclei The Gaucher cell is much larger and often has many nuclei The Niemann Pick cells usually do not stain positively with the customary fat stain, Sudan III or Nile blue sulphate However, after mordanting the frozen sections in potassium bichromate, the cytoplasm is filled with

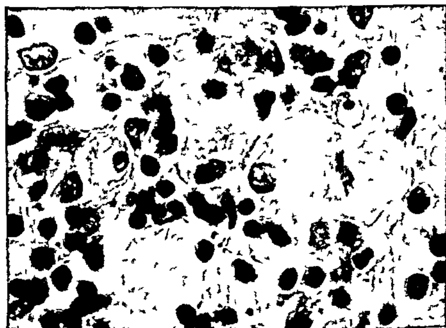


Fig 120 High power magnification of Niemann Pick cells Note the foamy appearance of these cells in contrast to the opaque Gaucher cells (Fig 103) (Through the courtesy of Dr Sidney Farber Pathological Department of the Childrens Hospital Boston)

granules that stain bright yellow with Sudan III and deep lavender with Nile blue The foam cells show the characteristic blue black color with Lorrain Smith-Dietrich stain which is supposed to be characteristic for sphingomyelin (For differential stain for Gaucher s disease and Niemann-Pick s disease see section Diagnosis in Part IV, Gaucher s Disease) Anisotropic bodies are observed in some of the cells although the fatty substance is for the most part isotropic The xanthoma cell and the Niemann-Pick cell are both foamy in structure and differ in this respect

Thannhauser Benotti and Reinstein[68] analyzed the organs in one case of Niemann Pick's disease with their method of quantitative sphingomyelin determination The following figures are based on dry weight (Table XLVI)

In contrast to the organs the serum does not show high phosphatide content The phosphatides in the serum have not been differentiated However the figures of total phosphatides of the case analyzed (Baumann) showed low phospholipid content In Baumann's case which has the most elaborate figures the total phospholipid content of the child's serum was 56 (normal 100-250 mgm /) Even if it is assumed that these phospholipid figures which represent the content of lecithin cephalin and sphingomyelin together, indicate only sphingomyelin this figure shows that there is not an increase of sphingomyelin in the serum

ANALYSIS OF SERUM OF BAUMANN'S CASE

Total cholesterol	164–191 mgm /	
Free cholesterol	94	
Cholesterol ester	70	
Total phospholipids	56	(normal 100-250)
Neutral fat	701	(normal 0 150)
P	4 5–4 8	
Ca	101–106	
Mg	3 –3 5	
Na	305–310	
Cl	88– 96	
N P N	28	
Urea	2	
Uric acid	2	
PH	7 4 and 7 4	

Alkali reserve CO combining power 4 and 44/ vol CO

Thannhauser Benotti and Reinstein[68] with their method of sphingomyelin determination and partition of other lipid substances analyzed the serum of a 15 month old child through the courtesy of Dr Blackfan Children's Hospital Boston This analysis shows that the sphingomyelin is not increased in the serum and shows normal figures Ascitic fluid from the same child was also analyzed (see table below) and no measurable amounts of sphingomyelin were present

in infancy explains why the cellular disturbance of lipid metabolism takes place almost everywhere in the organism and is found in more organs than would be the case if the same disorder developed in adults such as in the chronic form of Gaucher's disease

The stored substance in the Niemann Pick cells was reported by early investigators (Siegmund[163], Pick[9], Bloom[11]) to be lecithin because of the high content of phospholipids The following table shows the content of total phospholipids or Niemann Pick organs in per cent of wet weight (Table XLIV)

TABLE XLIV

	Siegmund[63]	Brahn and Pick[12]	Bloom and Kern[11]	Corcan and others[14]	Epstein and Lorenz[21]	Sobotka and others[66]		Baumann[5]	Normal from Baumann[5]
						a	b		
Spleen	6 4	10 3	8 7	7 8	10 0	5 4	2 8	4 5	0 08–2 5
Liver	6 94	—	—	12 0	9 3	8 2	3 3	6 3	0 08–2 5
Brain	—	—	—	—	5 0	4 1	—	4 8	—

Klenk[3], however, analyzing the organs of Baumann's case (Table XLV) demonstrated that the phospholipid stored in the Niemann Pick cell is not the monoaminophosphatides, lecithin and cephalin but the diaminophosphatide, sphingomyelin In contrast to sphingomyelin lecithin is only slightly increased and cephalin not at all increased in the organs Cholesterol is found normal or slightly increased The content of neutral fat of the organs especially the liver is elevated

TABLE XLV

KLENK'S[35] ANALYSES

	Amount of fresh material		Fat and cholesterol fraction		Monoaminophosphatide		Crude sphingomyelin (protogan fraction)	
	Wet weight gm	Dried substance gm	gm	% of wet weight	gm	% of wet weight	gm	% of wet weight
Spleen	370–390	53 7	3 44	0 9	4 63	1 2	12 6	3 3
Liver	795–815	140 8	12 3	1 5	16 4	2 0	34 7	4 3
Brain	5,0–6 0	69 7	9 2	1 5	11 8	2 0	16 4	[illegible]8

TABLE XXXIIIa

	Serum	Ascitic Fluid
Total cholesterol	196 0	73 5
Free cholesterol	40 7	17 1
Ester cholesterol	155 3	56 4
Total phospholipid	278 0	90 0
Sphingomyelin	4 0	0 00
Cephalin	8 0	34 7
Lecithin	46 0	55 3
Total fatty acids	614 0	130 0

Sphingomyelin isolated from normal liver and spleen as well as from Niemann Pick visceral organs contains according to Klenk[3] palmitic (C_{16})–stearic (C_{18}) and Lignoceric (C_{24}) acids Thannhauser Benotti and Boncoddo[68, 67] demonstrated that in pure sphingomyelin isolated with a new method from normal lung and spleen after the separation from hydrolecithin (dipalmitylecithin), only two saturated fatty acids are present in the molecule namely palmitic (C_{16}) and lignoceric (C_{24}) These acids are saturated fatty acids in acid amide linkage with sphingosin—NH—CO—R Sphingomyelin isolated from normal brain according to Walz[70] contains palmityl—stearyl—lingoceryl—(saturated C_{24}) and nervonic (unsaturated C_{24}) acids Thannhauser and Boncoddo[68c, 68d] separated hydrolecithin also from sphingomyelin isolated from normal brain After this separation pure brain sphingomyelin contained only stearic—lignoceric—and nervonic acids Klenk[3] claims that the sphingomyelin obtained from Niemann Pick brain is almost pure stearyl sphingomyelin Thannhauser and Boncoddo[68, 68d] found in brain sphingomyelin of Niemann Pick s disease after separation from hydrolecithin (dipalmitylecithin) mainly stearic acid but also small quantities of nervonic acid as a component while lignoceric acid could not be identified These analyses show that sphingomyelin of normal visceral organs and of Niemann Pick visceral organs are with respect to their component fatty acids only quantitatively but not principally different

Sphingosin isolated after acid hydrolysis of sphingomyelin derived from normal as well as Niemann Pick organs has a low iodine number which signifies that the sphingosin in the sphingomyelin molecule is a mixture of saturated and unsaturated sphingosin a fact also demonstrated by Carter and coworkers for sphingosin derived from cerebrosides[12, 16] For the pathogenesis of Niemann Pick s disease these analytical findings are important because they demonstrate that sphingo-

TABLE XLVI

	Niemann Pick spleen mgm %	Normal spleen mgm %	Niemann Pick kidney mgm	Normal kidney mgm %	Niemann Pick liver mgm %	Normal liver mgm %	Niemann Pick brain mgm %	Normal brain mgm %
Total cholesterol	6 73	1 8–2 4	2 8	1 4–2 8	7 00	2 0–2 6	6 45	7 3–15 0
Free cholesterol	6 70	1 0–1 1	2 81	1 0–1 1	4 50	0 4–0 5	5 43	1 3–4 6
Ester cholesterol	0 03	0 7–1 3	0 01	0 5–1 7	2 50	1 5–2 2	1 02	6 1–10 3
Total phospholipids	4 5	5 5–11 0	41 5	7 0–10 0	37 1	9 0–11 0	61 0	25–35
Sphingomyelin	3 70	0 7–1 0	9 35	0 6–0 8	25 90	0 3–0 5	4 84	4 5–7 0

lism If Pick's assumption of a general disturbance of the intermediary sphingomyelin disintegration is correct a substantial increase of sphingomyelin should result in the serum The reticulum cells and the histiocytes play only a passive role Infiltration and storage occur because the amount of the respective lipid in the blood is above the physiological level

Opposed to this theory is the assumption that the reticular as well as the histiocytic and macrophagic cells are primarily and actively involved in the etiology of the disease Although they do not contain large amounts of fat under normal conditions it is believed that just these cells play an important part in the metabolism of fats and lipids

Schlagenhaufer[81] characterized Gaucher's disease as a systemic constitutional disease of the lymph hemapoietic apparatus The cellular hyperplasia of the reticular cells was assumed by later investigators to be due to a dysfunction of the cells which are able to take up lipid substances from the blood It was believed that these substances which could not be discharged accumulated within the cells and blockaded the cells giving them their characteristic macrophagic appearance It was, therefore concluded that a similar process only one which is more extensive and involves the reticulum as well as the organ cells should be the etiology of Niemann Pick's disease in which the phosphatides and to a lesser degree the sterols are retained within the cells

At the time when the monoaminophosphatides especially lecithin, were assumed to be stored in the Niemann Pick cells Sobotka[86] characterized the disturbance as a deficiency of the esterases that is an inability to convert the fatty acid esters of lecithin and cholesterol to neutral fats However the fact that increased neutral fat is found in the liver and spleen as well as in the serum of infants with Niemann Pick's disease is not in conformity with such a hypothesis

The observation that sphingomyelin and to a slight degree cholesterol are increased in the Niemann Pick cell led Baumann [6] to study the cholesterol metabolism in one of his cases The findings for the cholesterol balance were negative He therefore concluded that the increase of sterols in the Niemann Pick cells is not due to an increased supply from the blood stream (the concentration of cholesterol in the serum of his case was normal that in cases of other authors was slightly increased) but to an increased synthesis of cholesterol within the cell Analogous to the increased sterol synthesis within the cell Baumann believes that there is an increased synthesis of the phosphatides especially of sphingomyelin which is etiologically characteristic of Niemann Pick's disease

myelin found enormously increased in Niemann-Pick's disease is with regard to its chemical constitution not principally different from that in organs of healthy individuals

Theories of Pathogenesis

Niemann-Pick's disease is characterized by an enormous accumulation of lipid material in histiocytes and macrophages as well as in reticular cells of all organs This lipid material consists essentially of the diaminophosphatide, sphingomyelin A slight increase of fat and cholesterol is found also in the affected organs The monoaminophosphatide lecithin is slightly increased while cephalin is not elevated in these cells The blood serum, however, does not show an increase of sphingomyelin Cholesterol and neutral fat are slightly increased in the serum in a few cases Parallel with the content of neutral fat the serum sometimes may show slight hyperlipemia

Any explanation of the pathogenesis of Niemann-Pick's disease must be based on these findings, especially the fact demonstrated by recent investigations that the high sphingomyelin content of the organs does not correspond with the normal content of sphingomyelin of the circulating blood

As in the case of xanthomatosis and Gaucher's disease many different suggestions have been advanced to explain the mechanism of the disturbance in Niemann Pick's disease One of these, which has been proposed by Ludwig Pick himself, is mentioned in most of the discussions and case reports He assumes the existence of a primary constitutional metabolic disturbance in the intermediary metabolism of the sphingomyelins As a result of a disturbance of the intermediary sphingomyelin metabolism Pick assumed an increase of this substance in the serum In his opinion the sphingomyelin should infiltrate the tissue cells similar to that observed in lipid feeding of animals or in cases where vital dye has been injected experimentally

Pick accepted Epstein's suggestion that the increase of sphingomyelin in blood and issue is the result of an insufficient disintegration of this substance in the intermediary metabolism like cystin in cystinuria According to Pick, the accumulation of sphingomyelin in the cells therefore is a secondary process The primary distubance should be in the intermediary metabolism and not in the cells themselves The cells concerned are only the storage place for the sphingomyelin which is not disintegrated in the intermediary metabo

enzymatic systems in question contain cerebrosidases and specific phos phatases An unbalance of these enzymes within the cells is assumed to be the underlying mechanism of Gaucher s disease on the one hand and Niemann Pick s disease on the other The following diagram attempts to picture the unbalance of the enzyme action in Niemann Pick s disease

It has not been clarified whether the synthesis of a sphingomyelin is increased or the splitting of sphingomyelin is decreased within the cell It is the unbalance of these enzymes which leads to the accumu lation of sphingomyelin characteristic of Niemann Pick s disease Since sphingomyelin in Niemann Pick's disease and cerebrosides in Gaucher s disease are not increased in the serum but are accumulated only within the affected cells the author concluded that the cause of Niemann Pick s disease as well as Gaucher's disease is an intracellular dysfunction due to an unbalance of enzymes within the affected cells *With this conception the emphasis is placed on the enzymatic dysfunction of distinct cells as the pathogenic factor of a group of lipid diseases, which become evident by the accumulation of lipid substances within the cell* Pick s conception that the accumulation of sphingomyelin is caused by an infiltration of the cells (from the blood stream) is no longer valid because the sphingomyelin content of the serum in Niemann Pick s disease is not increased but normal In Niemann Pick s disease sphingomyelin analogous to the cerebrosides in Gaucher's disease is formed and deposited within the cells where it is found

A INFANTILE FORM OF NIEMANN PICK S DISEASE

Clinical Course

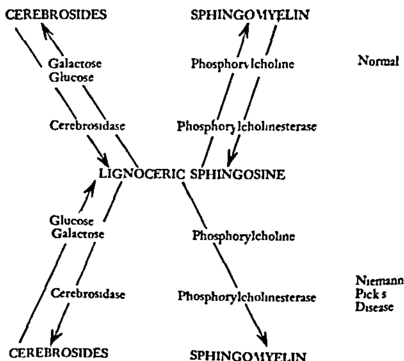
In Gaucher s disease the chronic adult form prevails while the acute infantile form is rare In Niemann Pick s disease the infantile form is the common one of the disorder its occurrence in adults is exceptional The infants reported usually do not survive the second year of life

Strikingly characteristic symptoms are present in all cases In contrast to the emaciated extremities which show only traces of sub cutaneous fat the abdomen is enormously distended as a result of the enlarged liver and spleen

The onset of the disease is insidious The infants usually are born at full term and with normal weight (see picture of twins described by Freudenberg Figs 123 and 124) Their development in the first

However, it does not seem likely that the slight increase of cholesterol and neutral fat in these organs is basically concerned with the mechanism causing the accumulation of sphingomyelin within the cells

Thannhauser and his coworkers[6] demonstrated that the close physiological relationship of cerebrosides and sphingomyelin is based on the group of substances called ceramides, which are common to both and contains sphingosin and a fatty acid in an acid-amide (NH–CO–R) linkage Lignoceryl sphingosin, which is one of the ceremides is found, according to Fraenkel, Bielchowsky and Thannhauser[6], in normal liver and spleen Sphingomyelin is derived from such a ceramide lignoceryl sphingosin, by esterification with choline and phosphoric acid Cerebrosides on the other hand, are built from the same ceramides by glucoside formation with galactose or glucose These authors suggested that cerebrosides on the one hand and sphingomyelin on the other are formed from ceramides such as lignoceryl sphingosin substances common to both by an enzymatic system within the cell which is balanced by certain activating and inhibiting substances The



exactly They may occur as early as the first month and as late as the fifth month but not later than the ninth month The infants become thin and emaciated (Fig 121), and their growth is retarded The abdomen becomes enlarged The enormous liver and spleen are felt upon examination The skin (Figs 121 1 4), which becomes dehydrated attains a waxy appearance A yellowish brown tint is especially noticeable on the exposed parts The superficial lymph nodes increase more or less in size At the height of the disease the infant is apathetic The eyes are turned upward, most of the time so intensively that only the white of the sclerae are visible The mouth is open and the tongue protrudes slightly The face has a mongoloid expression (Figs 121 and 1 4) The infant loses the ability to sit up and hold its head up high In late stages there is complete idiocy Most of the motor and psychic functions are lost There are usually no changes in the tendon reflexes nor is there the sign of Babinski The muscles are flabby There are no spasms or laryngeal crises The emaciated extremities have a decreased tone and are scarcely moved Vomiting increases the dehydration Usually edema of the ankles and eyelids appears finally This may be observed also in earlier stages In the later stages fever simulates infectious disease The fever usually may be explained by the involvement of the lungs in the disease The disease progresses rapidly The infant becomes completely debilitated mentally and physically until his death results

Clinical Case

Case L—The clinical course in the disease in a o month old child is described by Baumann[5] According to the report of the parents the development of the child was fairly normal but not so good as that of the other children From the time of the child's birth his skin had been very pale When he was between 9 and 10 months old, his abdomen began to become distended Between 8 and 14 months the child was able to sit up independently He kept his head aloft and moved his extremities When the child was thirteen months he did not have any appetite and lost weight He was unable to laugh His spontaneous motions lessened he could not sit up or move his head The size of the abdomen grew steadily larger while the other parts of his body became more emaciated

When he was admitted to the hospital at twenty months he weighed 7 oo grams Before he died he weighed 6 900 grams The maintenance of this weight was only possible because of the hospital care His diet consisted of 600 grams of whole milk 30 grams of sugar oo grams of banana and some mashed potatoes vegetables and cereals Feeding the child was



Fig 121 Niemann Pick's disease Note mongoloid expression protruding tongue enlarged lymph nodes and pigmented spots on the arms and legs (Reproduced from Baumann T and associates[6])

weeks and months apparently is normal However, they gradually stop eating their regular meals and begin to lose weight continuously The time of the onset of these digestive disturbances has not been determined

globin red blood cells 4 000 000 white blood cells 5 200 eosinophiles 6/ basophiles 1 staff 3 segmented 4 lymphocytes 4 monocytes 4 reticu lum cells 3 platelets 160 000

Intensive perspiration and saliva formation were observed from the be ginning until the end of the disease The stools and the urine did not show any abnormal findings

Until the child had reached the 24th and 25th months his temperature had been normal At that time an intercurrent high temperature was ob served It was probably due to lung involvement When the child was between 5 and 7 months old the temperature was again normal The child died in the 27th month of an intercurrent bronchial pneumonia

Clinical Features

Incidence —About seventy cases of this affection have been recorded up to 1947

Distribution —With increasing knowledge of the disease it does not seem to be so extremely rare Since cases have been reported from all over the world a special distribution does not seem to exist

Sex —It was believed that the female sex is more afflicted than the male It seems however that the sexes do not differ in their susceptibility to Niemann Pick s disease

Race —There is a predisposition to this disease among the Jewish race The proportion of Jewish to non-Jewish infants reported is about three to one As far the author could ascertain there is no case reported in the colored race Since Gaucher s disease has been observed in the colored race there is no doubt that there will also be cases of Niemann-Pick s disease among negroes

Age —It was believed that the disease occurs only in infants none of whom lived beyond the second year The shortest lifetime was seven months the longest was twenty seven months There are however now cases on record of Niemann Pick s disease in a 4 year old girl (Glanzmann[7b]) in an 8 year old boy (Farber and Thannhauser[4]) and in two brothers 9 and 33 years of age (Dusendschon[17b] Pfandler[47]) Pfandler examined 14 other members of this family and believes but does not prove that ten other members of two generations had signs (micro-symptoms) of the disease

Familial Occurrence —There is a familial tendency of this affection Several cases have been reported (Knox Wahl and Schmeisser[40] Ham burger[0] Dienst and Hamperl[1]) where siblings of the same family died of the disease with an enlarged spleen and liver Sphingomyelin was not

very difficult because he kept food in his mouth without swallowing it This is a feature observed in mentally backward children During the last few weeks the child vomited frequently Baumann[5] thought that the vomiting was of cerebral origin

The lack of motion and immobility increased during the child s hospital stay At the age of twenty two months he no longer made any spontaneous motions nor noticed anything brought to his attention He kept his eyes in a fixed position He was completely deaf and did not react to noises He was unable to move his jaws spontaneously, and if he was given a bottle the nurse had to stimulate the movements Although he whimpered at first, he was unable to make even these sounds in the last few months

There were no pupillary reactions, either to light or accommodation There was also no corneal reflex, the eyelids were half closed The tendon reflexes, which were increased at first could not be elicited after the child was twenty two months old The muscles were hypotonic up to the time of the child s death

The skin had a grayish brown tinge, especially on the face hands and feet This kind of pigment was scattered diffusely over the entire body even on the scalp The hair on the scalp was scant coarse and thick very similar to that found in cretins The subcutaneous fat tissue on the face buttocks and legs had almost entirely disappeared and remained unaltered only on the cheeks which protruded

The child s mouth was open and stuffed by the tongue There was a constant flow of saliva No changes were found in the mucous membrane The teeth which at first were well formed lost their dentine and became loose in the alveoli The gums which were always slightly inflamed had a tendency towards bleeding When the child was twenty three months old he showed lung symptoms Rhonchi over both lungs were heard These were indicative of diffuse bronchitis The x ray picture of the lung revealed scattered small spots over both lung fields like those found in miliary tuberculosis The respiration of the child continuously increased until his death

The heart did not show any signs of disease The liver and spleen, which were markedly enlarged were very firm in consistency The abdomen was enlarged There was diffuse lymphadenopathy The consistency of the lymph nodes was very firm

The peripheral bones were sensitive to pressure The x ray pictures showed osteoporosis The bone nuclei of the metacarpal bones were already present when the child was eighteen months old The epiphyseal nuclei however, did not appear until he was twenty five months old No rickets were present The x ray pictures of the long bones did not show bone changes like those found in Gaucher s disease or pseudo cystic changes like those of zanthomatosis of the bones

The child was slightly anemic Blood examination revealed 73% hemo

congenital, familial systemic disorder of the intracellular metabolism In Part I the author presented a scheme demonstrating that lignoceryl-sphingosin is the basic substance for the formation of cerebrosides (lignoceryl galactoside) on the one hand and sphingomyelin (lignoceryl sphingosin choline phosphoric ester) on the other In the light of the chemical relationship of these three substances it seems logical to explain the deviation from the normal lipid metabolism within the reticular cell as an



Fig 123 Rapid progression of cachexia in Niemann Pick s disease in twins, 1 year 4 months (E. Freudenberg 272)

unbalance of intracellular enzymes concerned with the disintegration and synthesis of these substances As a result there is a one sided accumulation of one of these substances which in Niemann Pick s disease is sphingomyelin The fact that the total cholesterol in the organs is increased in comparison with the cholesterol in the normal organs seems to be a secondary feature

Skin —There is a complete disappearance of the subcutaneous fat tissue of the extremities The skin which is wrinkled and pale is like a plastice mass (see Fig 124) Profuse sweating which occurs may last

isolated in any of these familial cases E Freudenberg[27a] reported the cases of two sets of twins (Figs 122 and 123) with Niemann Pick's disease in which L Klenk determined the sphingomyelin in the organs[3] Because of the similarity with the infantile form of Gaucher's disease, which also occurs in brothers and sisters, chemical analysis is necessary for future exact identification of Niemann Pick's disease

Constitutional Factors—The constitutional character of Niemann Pick's disease is shown by its prevalence in the Jewish race Further



Fig 122 Niemann Pick's disease in twins 1 year old (E Freudenberg 27a)

evidence of the constitutional character of the disease is the possible simultaneous occurrence of amaurotic idiocy, Tay-Sachs' syndrome itself a constitutional disorder Malformations, such as microgyria and polydactylia which are observed in some cases, also indicate a familial degenerative disease The manner in which the disease is transmitted is not definitely known A simple recessive transmission was suggested Pfandler[47] believes that the transmission in Niemann Pick's disease is irregularly dominant with a tendency to manifest itself in males

Etiologically Niemann-Pick's disease is a constitutional, probably





FIG 1 4 [redacted]—Niemann Pick's Disease Case observed by the author Note the mongoloid expression protruding tongue with blue black spots enlarged glands and *pigmented areas on the arms*

during the entire course of the disease There is a gray-brown yellowish diffuse pigmentation especially on the places exposed to light The pigmentation, is not a derivative of blood pigment or bilirubin but is due to an increase of normal skin pigment that is, melanin One case verified by analysis of the organs by the author also showed pigmentation of the mucous membranes of the mouth In addition two dark black-blue spots were seen on the surface of the tongue and on the gums These large black-blue spots, so called mongolian spots are observed in heredo degenerative disorders, but are not characteristic of this disease The pigmentation may be due to the infiltration of the adrenals by Niemann Pick cells which replace the tissue of the normal adrenal medulla The nature of the pigmentation may, therefore, be similar to that found in Addison s disease

Skeletal System—Bone lesions, patchy decalcifications usually are not found by x ray films despite the fact that the bone marrow is affected This may be explained by the fact that Niemann Pick s disease occurs in early infancy However, the skull as well as the long bones shows slight osteoporosis in the x-ray pictures Bone resorption in patchy areas is reported at autopsy only by Poncher[51] Rickets does not occur The bone formation is more advanced The metacarpal bones already show definite osseous tissue when the infant is fourteen to eighteen months old The chemical analysis of the bones (Baumann[5]) shows normal composition of calcium and inorganic phosphorus

Lymph nodes—The peripheral lymph nodes usually are moderately enlarged The consistency of the lymph nodes is rather firm

Lungs—The respiration is increased sometimes is audible The infants frequently have bronchitis and coughing The tendency to small pneumonic infiltrations of the lung with elevation of temperature is attributed to involvement of the lung in the disease The x-ray picture of the lungs is very similar to that of miliary tuberculosis Hundreds of small nodules are scattered over both lung fields The small miliary nodules which are visible in the x-ray films result from the fact that almost all alveoli are filled with Niemann-Pick cells (Figs 116 and 117) The inter-alveolar septa and the periadventitial tissue also show an accumulation of lipids with Niemann-Pick stain A more diffuse pneumonitis-like infiltration visible by x-ray is also reported Postmortem examination reveals that the bronchi are filled with phlegm which contains leucocytes and Niemann Pick cells If it is possible to examine the sputum the diagnosis of Niemann Pick's disease could be made from the presence of these cells in the bronchial phlegm

Heart —The action of the heart is increased during the disease There are no other clinical symptoms to suggest the presence of Niemann Pick cells between the muscle fibers and in the nerve sheaths of the nervous tissue of the heart

Gastrointestinal Symptoms —One of the earliest symptoms is the child s refusal to swallow food accompanied by vomiting The profuse vomiting however may be a central symptom The ferments of stomach and intestines as well as the bile and pancreatic juice are normal (Baumann[5]) Niemann Pick cells intersperse the mucosa of all parts of the intestines These anatomical changes however do not interfere with the normal digestion If the infant is fed with the right food dyspepsia is not a symptom

Spleen and Liver —The abdomen is enormously distended The liver and spleen fill the abdomen almost completely (Fig 115) The enlargement of these organs may appear very early even in the first weeks after the birth of the infant These organs are hard and firm and their edges are somewhat thickened The notch of the spleen is distinctly palpable The macroscopic appearance of the liver which is yellowish white resembles that of a fatty liver The function of this organ in regard to the bile production and other liver functions remains for a long time undisturbed despite the fact that its entire histological structure is completely altered by the accumulation of Niemann Pick cells The structure of the spleen likewise is changed The pulp is almost entirely replaced by Niemann Pick cells

Kidney —The urine does not contain albumin or sugar The sediment rarely contains cells which resemble foam cells

Endocrine Glands —Despite the fact that all endocrine glands especially the thymus the adrenals and the pancreas are interspersed with Niemann Pick cells there is no clinical feature except the abnormal pigmentation which might suggest endocrine disturbance

Nervous System —The signs of organic nervous disease initiate the onset of Niemann Pick s disease The muscles become weak The infant can no longer sit erect or hold up its head It takes little interest in its surroundings and never reaches for toys or calls for food The tendon reflexes are normal or slightly increased A moderate degree of spasticity is observed at the onset but later the muscles are flabby and hypotonic Mental dullness increases until psychic and motor functions are almost totally lost The infant finally lapses into a state of complete idiocy

Eyes —A cherry red spot in a grayish green halo which occupies the place of the macula lutea is found in several cases This condition is

Serum Chemistry—For serum figures (see Table XXXIIIa) The most important finding is that the total phospholipids in the serum are low Despite the enormous increase of sphingomyelin in the organs there is definitely no increase in the serum The total cholesterol is not increased or slightly increased The ratio of cholesterol to cholesterol ester may be normal or reversed Neutral fat is slightly increased The serum may be slightly lipemic However hyperlipemia is not a constant feature The diagnosis of Niemann Pick's disease cannot be made by lipid analysis of the serum

Ascitic Fluid—Ascites is not a regular feature but it sometimes occurs especially in later stages of the disease The ascitic fluid is not lipemic The results of ascitic fluid analysis are helpful for comparison with those obtained from an analysis of the serum because they show the same low figures of phospholipids (see Table XXXIIIa) The low figure of sphingomyelin in the serum as well as in the ascites fluid decisively proves that the sphingomyelin is only increased in organ cells and not in the body fluids

Protein and Carbohydrate Metabolism—Baumann[5] has contributed the only figures pertaining to these functions He found protein as well as carbohydrate metabolism normal Despite the dehydration the mineral balance also showed normal figures Baumann[5] believes that increased basal metabolism and increased insensible perspiration are due to cerebral disturbances

Diagnosis

The diagnosis of Niemann Pick's disease can be made with certainty only by chemical or histological examination of the diseased tissue The biopsy specimen may be obtained from a lymph node or by bone marrow biopsy or bone marrow puncture The bone marrow biopsy is more advisable than the splenic puncture The unstained Niemann Pick cell has a characteristic vacuolated foamy appearance entirely different from that of the opaque homogeneous Gaucher cells with their delicate network Sometimes the xanthomatous foam cell may have a similar appearance to that of Niemann Pick cells However the Niemann Pick cell is larger in size sometimes containing two or three nuclei It gives a characteristic staining with Smith Dietrich stain The definite diagnosis can only be secured by chemical analysis of the material obtained by biopsy

Sphingomyelin estimation for clinical diagnosis can be carried out in small amounts of tissue by the method of Schmidt Hershman Benotti

similar to that found in amaurotic idiocy, Tay-Sachs' diseases The eyesight diminishes with the progression of the disease until the infant no longer reacts to light

Ear —Inner ear deafness develops in almost all cases In later stages the infant does not react to voices or sounds

Blood —A moderate microcytic anemia is found with hemoglobin 45 to 80% and red blood cells -,500,000 to 3,900,000 White blood cells vary between slight leukocytosis 12-20,000 and moderate leukopenia 3-5000 Platelets range from 150,000 to 400,000 Some erythroblasts and polychromatophilia may be found The occasional finding of foam cells

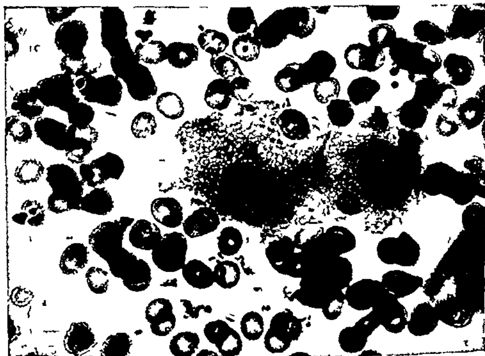


FIG 125 Niemann Pick's disease Giant reticulum cells in the blood (Reproduced from Baumann and associates[6])

in the peripheral blood is of great importance for the diagnosis (Baty[4], Poncher[51], Baumann[5] (Fig 1-5) Gaucher cells in contrast are not found in the blood It is evident that the foam cells described by Poncher[51] and Baumann[5] are identical with the vacuolated white blood cells observed by Baty[4] Baumann[5] also reports the presence of reticular giant cells and basophilic reticulum cells in the blood stream Clotting time and bleeding time are normal

The only infantile disease which is difficult to distinguish from Niemann-Pick's disease is the acute infantile form of Gaucher's disease. In both diseases the development of the disease usually starts in the first six months of the infant's life and progresses rapidly until extreme cachexia and mental deterioration result in death. Clinically pigmentation and cherry red spot in the retina are present only in Niemann-Pick's disease. There is also a marked difference in the nervous syndrome of both diseases. In the infantile form of Gaucher's disease the spasticity is more pronounced and the arms and hands are flexed. There is definite opisthotonus and strabismus. Spells of cyanosis and crises of laryngospasm signify the participation of the respiratory muscles in the spasmodic complex. *Infants with Gaucher's disease have features like an animal with cerebral decortication.* In Niemann-Pick's disease, on the other hand, the infant has only slight rigidity of the muscles at the onset. In the course of the disease flabbiness and lack of tone of the muscles are found. There is no opisthotonus or trismus or laryngospasm present. The Niemann-Pick infant has a mongoloid expression, open mouth and protruding tongue. The Gaucher infant does not have these signs, but *marked strabismus has been present in all cases observed.*

The blood chemistry does not help very much in the differential diagnosis because neither sphingomyelin nor cerebrosides respectively are increased in the serum. Yet in Niemann-Pick's disease the total fat and total cholesterol are high normal, while in acute infantile form of Gaucher's disease the total fat and total cholesterol are low normal.

In Niemann-Pick's disease, in contrast to acute infantile Gaucher's disease, foam cells and vacuolated cells sometimes are demonstrable in the blood smear. The decisive factor for differential diagnosis is a biopsy of a lymph node or bone marrow puncture or biopsy. (For the important differences in *appearance and staining of Gaucher and Niemann-Pick cells* see Table XLIII.) Chemical determination of sphingomyelin and total phospholipids as well as estimation of cerebrosides in biopsy material should be attempted in all cases for differential diagnosis.

Prognosis and Treatment

The prognosis is definitely grave. Death usually occurs in the second year. There are no reports of infants who have lived until the end of the third year where the disease had already been *recognized in infancy.*

and Thannhauser[61a] With this method also the figures for total phospholipid content of the tissue and serum are obtained When the sphingomyelin content of the examined organ is increased several times over the normal value, the diagnosis of Niemann Pick's disease is secured The chemical analysis should be carried out always on dry organs which are brought to constant weight The chemical analysis of the serum does not show any *increase of phospholipids, its analysis cannot be used for the* diagnosis of the disease The increase of cholesterol in the serum is not constant and not significant Hyperlipemia is not present in most of the cases, and when it is present, it is found only to a moderate degree Neutral fat may be slightly increased The chemical blood findings, therefore are not helpful in making a diagnosis of Niemann-Pick's disease It must be emphasized again that neither Gaucher's disease nor Niemann Pick's disease show an increase in the serum of the chemical substance at fault i e sphingomyelin in Niemann Pick's disease or cerebroside in Gaucher's disease The finding of giant reticulum cells, of vacuolated foam cells and basophilic reticulum cells in the blood smear are according to Baumann[5] specific for Niemann-Pick's disease and may be helpful for the diagnosis

The recognition of Niemann Pick's disease by only clinical symptoms must take into consideration the fact that Niemann Pick's disease is predominantly an affection of infancy which progresses rapidly and is frequent in the Jewish race Extreme cachexia combined with blindness and deafness idiocy and spleno hepatomegaly are the decisive clinical symptoms of the infantile form of the disease

Differential Diagnosis

In early infancy slight enlargement of the spleen is not infrequent Enlargement of liver and spleen however, is found only in pathological conditions In such cases congenital syphilis, familial anemias of infancy erythroblastic anemias may be considered The blood picture at once permits the differentiation of these diseases from Niemann-Pick's disease Large liver together with severe lipemia is found in glycogen storage von Gierke's disease However in von Gierke's disease only the liver is found enlarged and not the spleen A severe hyperlipemia like that found in von Gierke's disease is never found in Niemann Pick's disease The blood sugar in Niemann Pick's disease is normal, in von Gierke's disease it is below normal

as a possible adult case of Niemann Pick's disease because of the chemical analyses of the organs involved However the phospholipids in the analyzed organs were not increased This case has been mentioned already as belonging to the group of reticulo endotheliosis (Letterer-Siwe) There remains therefore only the four above quoted verified cases of adult Niemann-Pick's disease

Clinical Cases

For a description of the clinical anatomical and histological features of this syndrome in adults publications by E Rutishauser A Dusendschon and U Pfandler concerning the cases of two brothers (Nestor A and David A) have been used and translated from the French

Case LI—Nestor A a 9 year old watchmaker died as a result of an accident on June 4 1938 His spleen was ruptured oo c c of blood were found in the abdominal cavity The diagnosis of Niemann Pick's disease was made after autopsy and histological examination of the viscera There is no further case history The patient apparently had never consulted a physician before his sudden death

Case LII—David A a 33 year old laborer worked in a mill He had always had a slightly yellowish discoloration of the skin Several members of the family supposedly had the same complexion He had been healthy until January 1940 when he entered the hospital at La Chaux de Fonds Switzerland for an acute bronchitis Splenomegaly was then discovered for the first time A slight jaundice was present also In 1939 he had already become short of breath and his legs would swell toward evening The amount of daily urine was small about one liter a day Because of a highly increased count of red blood cells and a hemoglobin of 118 per cent the physician at the hospital considered it to be Vaquez's disease Later in 1940 his physician sent him to the hospital again with the diagnosis of Banti's disease and polycythemia

Physical Examination—Weight is 58 kg., patient is of asthenic type of moderate height The nutritional state is poor The patient is severely dyspnic and deeply cyanotic A definite jaundice is present Both legs are edematous around the lower parts Heart shows gallop rhythm over the entire heart the sounds are clear Blood pressure is 130/80 The patient coughs Lungs show vesicular breathing no dullness but rales over both bases The x ray report reads as follows Both diaphragms are elevated and move very little Both sinuses are full The lungs show a symmetrical dense infiltration departing from both hilis Inspection of the film with the magnifying glass reveals a peculiar structure of this infiltration Small irregular patches are seen their size is variable mostly that of the head of a needle They are not definitely round and are sometimes like the marks of gun

Splenectomy, x-ray and radium therapy have been tried without success. Endocrine extracts have been given without changing the fatal course of the disease.

Hamburger[30] gave his patient a fat free diet in the attempt to influence the accumulation of fat in organs and blood. It was possible to decrease the serum cholesterol and the serum fat content by using this low fat diet. High fat and high cholesterol in the serum are, however, secondary occurrences in Niemann-Pick's disease. It was not possible to change the primary manifestation of the disease, that is, the accumulation of sphingomyelin within the cell. This is obvious, because Niemann-Pick's disease is a cellular disease in which the intracellular metabolism certainly can not be corrected by a fat-free diet. On the contrary, the physician should feed the child as long as possible by means of nasal tubage. Foods rich in calories, whatever they may consist of, should be given so that the patient may fight the rapidly progressing cachexia.

B. ADULT FORM OF NIEMANN-PICK'S DISEASE

Introduction

The opinion that Niemann-Pick's disease occurs only in infants and terminates in death within the first two years of life can no longer be maintained. Glanzmann [b] described the disease in an 8 year old girl. Farber and Thannhauser [1] found a considerable increase of sphingomyelin in an extirpated spleen of an 8 year old boy. Rutishauser, Dusendschon[17b] and Pfandler[4] in a histological and chemical study of the organs of two brothers, 29 and 33 years old, proved that there was an enormous accumulation of sphingomyelin in the enlarged liver and spleen of these patients. The fact that the occurrence of Niemann-Pick's disease in adults had already been suggested by autopsies of cases in the earlier literature (Pick[48, 0]) must be mentioned. However, these definitely do not belong to this group. Sapegno's case [4] of a 47 year old patient reported as Gaucher's disease was neither histologically nor chemically identified as Niemann-Pick's disease. The case of a twenty-two year old girl described by Babes, Aurol and Babes[3] as Gaucher's disease with accumulation of eosinophilic cells probably should be classified as eosinophilic xanthomatous granuloma (lipid granulomatosis Schuller-Christian's disease). Dusendschon[17b] quoted the case of a 20 year old female described by Bagenstoss, Rosenberg and Osterberg

The reticulum cells which are charged with lipids have an influence upon *the reticulum itself. The latter shows pointed ends in the neighborhood of* the foam cells besides the apparent multiplication of silver stained fibrils. This increase of the reticulum fibrils is the result of the atrophy of the liver cells.

The lipid loaded cells are the cause of the sclerotic changes in the spaces of Kiernan. One encounters in the sclerotic strands modified lipid cells of a fusiform cellular character. In the areas where the sclerotic changes are maximal the lymph channels are rare and the junction ducts are sprinkled with lipids. New formation of bile capillaries is observed also in these places.

There is indeed an annular cirrhosis analagous to a toxic liver cirrhosis *but not an inflammatory cirrhosis with increase of cellular elements in the* periportal spaces.

Summary of Findings.—In case LI the storage of phosphatides of various degrees was found in different cellular elements of the liver mainly in the Kupffer cells, in some places in the parenchymatous liver cells and to a lesser grade in the vascular endothelial cells. In addition an annular cirrhosis was present.

The histological examination of the liver of Case LI Nestor A. shows also although to a lesser degree an annular cirrhosis resulting from a sclerosing non inflammatory process which extended from the spaces of Kiernan. The phosphatide accumulation is seen mainly in the Kupffer cells but also in the parenchymatous cells of the liver as well as in the endothelial vascular cells as in Case LII.

In the spleen of Case LI and LII the reticulum cells are mainly involved in the process of phosphatide accumulation. While the endothelial cells show phosphatides to a lesser degree they however contain much pigment. The reticulum shows proportional hyperplasia. The trabeculae are slightly pointed because of the fibrotic transformation of islands of Niemann Pick cells.

The lungs of Case LI and LII show an intense participation in the disease process. Niemann Pick cells are present chiefly in the alveoli. They are derived from alveolar epithelium and endothelium. Interstitial and vascular fibrosis is found. Hemosiderin is demonstrable around the bronchi, the blood vessels and in the Pick cells. The mucous membrane of the bronchi is involved to a lesser degree in the process of phosphatide accumulation.

Lymph nodes show a diffuse infiltration with phosphatide containing foam cells. Not all lymph nodes are equally involved. In some instances the structure of the node is almost normal. The endothelial cells of the sinus are not affected by the disease in contrast to the reticulum cells of

powder This is the picture of an invasion of the lung parenchyma departing from the hilis which looks like a neoplastic or leucemic infiltration proceeding along the peribronchial and perivascular lymphatics"

The abdomen is distended Ascites is present The liver is enlarged and palpable three fingers below the costal margin The spleen is enlarged firm and moves while the patient is breathing The spleen extends to the middle line of the abdomen its inferior pole being felt above the umbilicus

Laboratory findings—Red blood cells 6 500 000, hemoglobin 108 per cent white blood cells 7 000 with neutrophile polynuclears 65 per cent lympocytes 32 per cent monocytes 3 per cent Serological reactions for syphilis are negative Bilirubin is 20 mgm per cent van den Bergh gives direct positive reaction Urine shows albumin 0 sugar 0 urobilinogen + + urobilin + urinary sediment shows a few leucocytes and a few granulate casts The feces are formed and only slightly colored

Nervous system—The patient is of moderate intelligence with movements normal and no sensory changes and no signs of changes of equilibrium and coordination Tendon reflexes are normal Abdominal reflexes are absent Babinski sign not present Pupils react to light and accommodation The patient died of cardiac failure 20 hours after his entry into the hospital

Morbid Anatomy and Histology—The liver of Case LI 29 × 25 5 × 7 cm has a gray brown surface The parenchyma is yellowish brown and of firm consistency The liver of his brother, David (Case LII) is enlarged and light brown in color The capsule of this liver presents two layers a superficial one formed by connective tissue of hyaline appearance and a deeper layer also composed of connective tissue which is however younger and shows foam cells dispersed in the subcapsular cirrhotic tissue In some areas the capsule shows depressions, departing from which strands of fibrous tissue penetrate into the liver parenchyma These fibrous strands from the capsule join other fibrotic strands coming from 'Kiernan s spaces The latter are more extensive and engulf the lobular structure of the liver Phosphatide containing foam cells stained with scarlet red are present in the neighborhood of the Kiernan s spaces They almost always originate from Kupffer cells The liver cells contain droplets of fat like substances apparently poor in neutral fat which are hardly visualized by scarlet red stain In slices of blocks fixed in paraffin the liver cells show vacuoles probably corresponding to their neutral fat content In other areas especially in the portal spaces the Kupffer cells show hemosiderin deposits visualized with Turnbull stain

The participation of the endothelial cells of the blood vessels in the process of lipid storage is remarkable Indeed the majority of them are still intact However there are some which already are filled up with phosphatide but they remain small like those in the spleen and show a more intense coloring with scarlet red than the foamy Pick cells

until a physician examining them for an intercurrent disease finds an enlarged spleen

An accident cause the rupture of the spleen of Nestor A (Case LI) and an autopsy revealed his disease for the first time He had never consulted a doctor In the case history no mention is made of the kind of accident causing the fatal bleeding of the ruptured spleen It is possible that a spontaneous rupture of the spleen occurred as is observed in several cases where the spleen had previously been diseased (malaria infectious mononucleosis Gaucher's disease) An insignificant accident may have definitely been the immediate cause but the spleen might not have ruptured had it not been diseased previously Indeed Nestor A probably died from his disease without knowing that he was sick

David A (Case LII) died of heart failure Niemann Pick's disease in its chronic form was discovered at autopsy In analyzing the clinical features of David A retrospectively one becomes aware that the heart failure *developed gradually and was accompanied by a remarkable increase* of red blood cells (erythremia) Such an incidence of erythremia and *heart failure occurs not infrequently in cases of pulmonary fibrosis in* occupational lung diseases (dust silicosis etc) in chronic inflammatory peribronchial fibrosis (sarcoid fibrotic tuberculosis) or in sclerosis of the pulmonary arteries (Ayerza's disease) In this author's opinion the heart failure and the erythremia of David A were also the result of pulmonary fibrosis which was revealed by x ray and was shown at autopsy to be due to an intensive involvement of the lung with Niemann Pick's cells resulting in fibrosis of the lung A similar pathological occurrence is observed in the lung in the generalized form of Schuller Christian disease (eosinophilic xanthomatous granuloma essential xanthomatosis of the normocholesteremic type) Although it has been known for quite some time that the alveolar cells filled up with lipids may block the alveolar lumina in both infantile Gaucher's and Niemann *Pick's diseases it was revealed for the first time than chronic lung in*volvement may occur also in the adult form of Niemann Pick's disease and result in fibrosis of the lung and chronic pneumonitis leading to erythremia and heart failure

Nestor A (Case LI) was only slightly jaundiced David A (Case LII) exhibited severe jaundice during the last month of his illness In both patients the liver was enlarged Portal congestion was manifested by a large amount of ascites in Case LII Histological study of the two livers revealed that Kupffer cells as well as parenchymal cells were involved in the Niemann Pick pathology and were crammed with sphingomyelin

the node Here, as in other organs, the grade of accumulation of the phosphatides varies from one cell to another and is demonstrable by different staining methods (scarlet red, Ciaccio) The endothelial cells of the blood vessels of the lymph nodes are scarcely involved

Kidneys show intact glomeruli In the tubular epithelium small drops of fat are visible In several areas of the interstitial tissue especially in the area of the pyramids, a few foam cells, comparable to those seen in the liver spleen and lungs, were dispersed In the pancreas Pick cells are not present in either case In the brain the ganglion cells are not as ballooned as in familial idiocy of Tay-Sachs There is a certain degree of cortical atrophy but no characteristic changes are found Unfortunately there is no report concerning the bone marrow or the bones

Chemical determination of the lipid content of liver, spleen and lungs is shown in Table XLVII

TABLE XLVII

Lipid Analysis of Liver and Spleen of David A (Case LIV)

	Spleen	Normal Spleen	Liver	Normal Liver	Lung	Normal Lung
Total cholesterol	4 6	0 6 5	3 8	0 6	7 6	1 7
Lecithin and cephalin	8 8	4 5 11 0	2 63	6 0-11 0	2 67	4 5 8 0
Sphingomyelin (impure)	36 9	—	30 1	—	34 0	—
Sphingomyelin (pure)	3 3	0 3 1 0	1 8	0 -0 5	2 1	1 0- 0
Neutral fat	10 6	1 0 3 0	5 35	1 4 4 0	5 0	—

Figures express mgm per cent of dry weight Analyses were made by Dr Favarger The normal figures according to Thannhauser and Reinstein

Clinical Course and Clinical Features

The study of Rutishauser, Dusendschow and Pfandler of these two brothers is of general pathological and clinical importance because of their unique clinical observations and histological findings It definitely proves the occurrence of Niemann Pick s disease in adults The adult and infantile forms of Niemann Pick s disease are as clinically different from each other as are the adult and infantile forms of Gaucher's disease Both infantile Gaucher s as well as Niemann Pick s disease terminate in early death after a rapid and disastrous clinical course involving the entire organism The adult form in contrast is not manifested by any spectacular complaints Usually the patients are unaware of their disease

until a physician examining them for an intercurrent disease finds an enlarged spleen

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In both instances an annular cirrhosis developed though to a lesser degree in Case LI An advanced annular cirrhosis, as already described in detail, was found in Case LII The question arises as to whether the cirrhotic manifestations in these two patients originated from the primary Niemann-Pick lesions, or whether the annular cirrhosis was an independent feature attributable to some other cause It is difficult to settle these questions since no analogous cases of chronic liver involvement of the adult form of Niemann-Pick's disease are available Not even the beginning of a cirrhosis is noted in infantile Niemann Pick s disease despite the severe involvement of the liver Annular cirrhosis also has not been reported in the adult form of Gaucher's disease For this reason it is hard to believe that an annular cirrhosis should originate only from Niemann-Pick lesions in the syndrome under discussion The two brothers were alcoholics David A according to the report of the local authorities indulged more than his brother Many members of the family were drunkards Their general nutritional condition was poor It is, therefore, possible that alcohol and poor nutrition were decisive factors in the origin of the annular cirrhosis in both brothers Probably the cellular derangement of the liver due to Niemann Pick's disease was an important precipitating factor but the alcohol and the nutritional conditions may have been responsible for the development of just this type of annular cirrhosis Whatever the explanation may be the two brothers had Niemann Pick s lesions and annular cirrhosis of the liver at the same time

In the case of David A the spleen also showed corresponding to the progressed liver cirrhosis advanced hyperplasia of the reticulum and fibrosis besides the Niemann-Pick lesions Clinically it is noteworthy that the size of the spleen is reported much larger in these adult cases than it is reported in the infantile form Information is lacking either from x-ray films or autopsy findings concerning the osseous system or bone marrow of these two patients Both brothers were apparently not too alert mentally ('pshychisme") but Nestor was a watchmaker and David worked all his life as a mill laborer While David s brain histologically did not show the characteristic Tay Sachs lesions, his ganglion cells were slightly ballooned The cerebellar atrophy would hint also of chronic alcoholism

A most interesting speculation is whether Niemann-Pick's disease in these adult cases has progressed slowly since infancy and did not spread as the infantile form usually does to all organs or whether Niemann Pick's disease is a later development in these adults and then has remained

s itionary It is known that in some instances constitutional diseases due to germ plasma defects i e gene defects may first become apparent in adult life One may therefore be inclined to assume the latter view point since both brothers lived a busy life without complaints before succumbing to the complications of the disease

Inheritance

U Pfandler[4] analysed the histories and examined brothers and sisters of Nestor and David A Death from an unknown cause took three male brothers and one sister in infancy and one sister at the age of 11 Two older sisters of 34 and 36 and a brother of 57 refused examination Two sisters 40 and 47 years old and one brother 51 years old had so-called microsymptoms of Niemann Pick s disease Two brothers Auguste and Robert 43 and 44 years old exhibited so called macrosymptoms Of 12 other brothers and sisters of one generation of Nestor and David A four brothers and sisters died in infancy one sister died at the age of 11 and seven brothers and sisters were alive In addition one cousin and five members of the second generation children of the older brothers and of the cousin were examined Of the second generation three males whose ages were 17 19 and 18 (the last the son of the cousin) and two females of 20 and 3 years had so called microsympt oms of Niemann Pick s disease The macrosymptoms of Niemann Pick s disease present in the brothers Auguste and Robert were as follows hepatosplenomegaly bilirubin 1 7 and 1 4 mgm per cent respectively The total fatty acids of Auguste and Robert were 685 mgm per cent and 712 mgm per cent respectively (normal 300 500 mgm per cent fasting) In Auguste the total cholesterol was less than 30 mgm per cent and 20 mgm per cent were present as esters in Robert the total cholesterol was 177 mgm per cent and 66 mgm per cent were present as esters The low figures of cholesterol in Auguste are surprising and should have been checked by control analysis

There remain only the brothers Nestor and David A from the examined family of 14 brothers and sisters in whom the presence of Niemann Pick s disease was definitely demonstrated by histological findings and chemical analysis In the other members of the family further histological and chemical examination of the organs but not the serum will decide the presence or absence of Niemann Pick s disease In analogy with Gaucher's disease the occurrence of Niemann Pick s disease in members of several generations of the involved family seems

possible The so-called "microsymptoms" of Niemann-Pick's disease are according to Pfandler slight deviations from the normal in figures for total fatty acids and low cholesterol in serum Neither the 'micro symptoms' nor "microsymptoms" of Pfandler seem to prove the presence of Niemann Pick's disease for the following considerations Both brothers, Auguste and Robert, exhibiting "microsymptoms", indulged in alcohol Robert was an occasional alcoholic, Auguste a severe alcoholic Their hepatosplenomegaly may have resulted from alcoholism Niemann Pick's disease as the cause of their hepatosplenomegaly, even if they were siblings of brothers with this disease, is not yet proven Their serum chemistry is not of value for the diagnosis since the diagnosis of Niemann Pick's disease as already discussed in detail cannot be made from the chemical analysis of the lipids present in the serum

The same statement holds the more true for the so called micro symptoms of Niemann-Pick's disease The slight deviation of fatty acids and cholesterol from the normal is insignificant for the diagnosis of the presence of Niemann-Pick's disease The only way to verify the diagnosis of Niemann-Pick's disease is histological and chemical analysis of a biopsy specimen of an involved organ as it was carried out in the cases of Nestor A and David A

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SUPPLEMENT

A INFANTILE AMAUROTIC FAMILY IDIOCY

Introduction and General Discussion

Infantile amaurotic family idiocy was described first by B Sachs[3] in 1887 The ophthalmological features of this disease had been published already in 1881 by the English ophthalmologist W Tay[33] Since then the clinical syndrome of morbid heredity has been well established It consists of progressive mental deterioration associated with blindness The changes in the retina are characterized by a cherry red spot within a grayish green halo The disease progresses to a fatal termination between the first two years of life It is often familial although not all of the children in a particular family are affected and those who are spared remain normal in their physical development Consanguinity of ancestors may be of some significance The disease occurs mostly in Jewish people

Four types of amaurotic family idiocy have been distinguished in the literature

(1) The infantile form (Tay[33] and Sachs[3])
(2) The later infantile form (Spielmeyer[3] and Vogt[35-41])
(3) The juvenile form (Bielschowsky[1])
(4) The adult type (Kufs[1])

The infantile form of amaurotic idiocy later designated as Tay-Sachs disease has aroused a special interest because of the similarity of nervous and retinal symptoms with those of Niemann Pick s disease Originally the disease was attributed to arrested cerebral development It was considered a degenerative process involving the ganglion cells of the brain Finally the disease process was regarded as a disturbance of the lipid metabolism of the nerve cell identical with or closely related to the disturbance of phosphatide metabolism in Niemann Pick s disease The articles of Schaffer[30] on the one hand and those of Pick and Bielschowsky[0] and Sachs[1] on the other hand reveal two different schools of thought on the pathogenesis of Tay Sachs disease Pick and Bielschowsky expressed the opinion that amaurotic family idiocy is a partial manifestation of Niemann Pick s disease Schaffer adheres to the belief that both diseases are entirely different entities which occasionally may combine (combined form) because of their genotypic relationship An exhaustive study of the pertaining literature is found

in the paper of Rothstein and Welt[2] These authors, on the basis of clinical and histological observations of their own cases, came to the conclusion that it would be better to reserve the term Tay Sachs disease for the cases in which only the central nervous system is involved and to apply the term Niemann-Pick's disease to cases in which visceral involvement is present, regardless of whether other changes in the fundus are present or absent" Rintelen[21] on the basis of a histological study goes even further He considers the retinal changes in Niemann-Pick's disease as different from those of Tay-Sachs' disease The macular changes are not specific for a certain disease but will be found if necrobiotic changes of the ganglion cells in the retina occur, which lead to an increase of its fat content"

Thannhauser Benotti and Reinstein[34] analyzed brains of Niemann Pick's and Tay-Sachs' disease for the various kinds of phospholipids and determined quantitatively the different lipids in the visceral organs of a child who had died of Tay-Sachs' disease (see Table XLVIII and XLIX) There was in contrast to Niemann-Pick's disease no increase of sphingomyelin in the analyzed visceral organs These findings are in agreement with the opinion that Niemann-Pick's disease and Tay Sachs' disease are two different clinical entities, even though the eye ground changes (red macular spots) are similar by ophthalmoloscopic inspection and ballooned ganglion cells are found by histological examination of the brain in both diseases (see photographs in the publication of Rothstein and Welt) E Klenk[10 13] however, isolated a new group of lipids from the brain in Tay-Sachs disease and thereby established a chemical difference between the normal brain and that in Tay Sachs disease These new lipids which contain sphingosin, galactose and glucose in glucoside linkage, neuraminic acid and fatty acids, were named 'gangliosides by Klenk The ganglioside content of the brain was found considerably elevated in Tay-Sachs' disease while there was only a slight increase in Niemann-Pick's disease It remains to be seen whether the increase of gangliosides in the brain is characteristic of Tay-Sachs' disease or whether it occurs also in increased quantities in other heredodegenerative diseases of the brain

Course and Clinical Features

The clinical and pathological features are described by Jacob L Rothstein and Sara Welt in their paper on "Infantile Amaurotic Family Idiocy" as follows

Course and Clinical Features — The onset of symptoms is usually 4 to 6 months of age although occasionally the beginning of the disease has been noted as early as the second or third month Rarely symptoms have begun even earlier Epstein reported a case[5] in which the onset of symptoms was in the second week of life and Schick dated the appearance of symptoms (hyperacusis) in a recently observed patient from the age of 4 weeks Occasionally the onset may be later (at 2½ years of age in the case of Hassin and Parmelee[8]) The first symptom noted as a rule is listlessness in a previously healthy and apparently otherwise normal infant Progressive muscular weakness develops gradually with a corresponding decrease in the volitional movements as a result of the loss of muscular power As time goes on the infant can no longer change its position and is unable to hold its head up or to sit erect even when placed in the sitting position Its grasp becomes weaker and finally it becomes helpless lying apathetically in its crib As this picture unfolds it becomes increasingly evident that the vision has become impaired finally blindness is quite apparent and the child takes no notice of its surroundings and fails to recognize its mother or nurse

With the progression of the disease into its later phases the hearing becomes unusually acute (hyperacusis) and at the slightest noise the infant may be startled even though it was apathetic and drowsy a moment before Late in the course of the disease other evidences of mental disturbance appear Bouts of explosive laughter occur and frequently in the terminal stages other symptoms may appear which overshadow the picture such as muscular twitches or convulsions and decerebrate rigidity The muscular twitches appear as clonic muscular contractions of the eyelids or of the extremities or as convulsions of a few seconds duration in response to external stimuli (auditory or tactile) Decerebrate rigidity is reflected in flexion extension rigidity and when the patient is in this position the Magnus de Kleijn reflex is observed Typical decerebrate rigidity in cases of amaurotic family idiocy has been described by a number of observers (Ostertag[19] Hassin[7] Magnus and de Kleijn[16] de Bruin[2] Dollinger[4] Marinesco and Radovici[17] In many cases of amaurotic family idiocy only some phases of decerebrate rigidity for example extension spasticity have been observed

The most striking clinical feature is the visual disturbance which is due to changes in the retina or nerve head All patients become blind Typically examination of the fundus reveals the characteristic cherry red spot in the macula lutea which has been so widely recognized that no detailed description need be given here In addition to the macular

in the paper of Rothstein and Welt These authors on the basis of clinical and histological observations of their own cases, came to the conclusion that it would be better to reserve the term Tay Sachs' disease for the cases in which only the central nervous system is involved and to apply the term Niemann-Pick's disease to cases in which visceral involvement is present, regardless of whether other changes in the fundus are present or absent" Rintelen [1] on the basis of a histological study goes even further He considers the retinal changes in Niemann-Pick's disease as different from those of Tay-Sachs' disease "The macular changes are not specific for a certain disease but will be found if necrobiotic changes of the ganglion cells in the retina occur, which lead to an increase of its fat content"

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Course and Clinical Features

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finding of optic atrophy or of other retinal changes in a child with both idiocy and blindness must cause the observer to consider seriously the likelihood of the patient s having infantile amaurotic family idiocy Similarly Hassin[6] emphasized the importance of suspecting the presence of the Tay Sachs syndrome in the case of any child in which there is an obscure lesion of the central nervous system and the cherry red spot is absent but decerebrate rigidity is a prominent feature

Pathology and Histology

Sachs[3] in his classic paper and more recently Schaffer[5, 6] Hassin[7, 8] Ford[6] and Jaffe[9] published exhaustive descriptions of the pathology and histology of the disease Rothstein and Welt summarize the typical findings as follows

'*Macroscopic Changes* The brain may show no gross changes and no malformation It usually seems hard to the touch and leathery in consistency At times atrophy of the convolutions is present Gaping of the fissures [7] for example the sylvian or the interparietal is reported fairly frequently The cerebellum is often very small and abnormally firm The occipital lobes may be greatly reduced in size leaving the cerebellum uncovered The ventricles are dilated The weight of the brain varies considerably It is normal in some cases and increased in others but in the majority of instances it is reduced It may range from 670 to 1 000 gm (in Bielchowsky s case 1 690 gm) On section the brain is hard Sachs stated that in his first case the brain was so hard that the knife grated in cutting This feature has been emphasized by many observers However the diagnosis of infantile amaurotic family idiocy must rest on the microscopic examination since the leathery consistency and gaping of the sutures noted macroscopically may likewise occur in cases of Niemann Pick s disease

Microscopic Changes Universal changes are observed in the ganglion cells throughout the entire central nervous system—in the hemispheres the brain stem the pons the medulla the cerebellum and the spinal cord as well as in the retina The cells are swollen and assume varied globular shapes they may be bottle shaped pear shaped or round The dendrites are swollen and are enlarged and balloon like in appearance The cell nuclei are well preserved and are displaced to the periphery although at certain stages they disintegrate The Nissl bodies (the stainable chromophil substance) may be normal but are found only in the area

changes, optic atrophy is frequently encountered Occasionally, no cherry red spot can be found, even after careful examination, but in such instances optic atrophy (Schlesinger Greenfield and Stern)[31] or some type of macular change (Koller[11], Mulberger[18], Wolfsohn[3], Schaffer[30], Ostertag[19], Hassin and Parmelee[8]) is present and seems to act as an 'equivalent' for the cherry red spot Some of these 'equivalents' have been described as follows a veil-like, milky bluish haze near the macula (Koller's case), a grayish nebulous appearance of the retina (Parmelee's case) and a reddish macula surrounded by a pigmented ring (Mulberger's case)

"In general at the onset and in the early stages of the disease the child seems healthy and well developed Schick has been particularly struck by the lovely, velvety smooth texture of the skin of such infants and the 'ironing-out' of the cutaneous linear markings He has expressed the opinion that this may be due to some so far unknown *qualitative* difference between the fat and the subcutaneous tissue of the patient with amaurotic family idiocy and those of the normal child Later in the course of the disease the child becomes marantic, it refuses its food, is unable to nurse and has difficulty in swallowing, which necessitates its being fed by gavage Emaciation develops rapidly in later stages Death usually occurs from marasmus or from an intercurrent infection after an average duration of illness of eighteen months or by the time the child is 2 years of age In a few cases a more protracted course results in a longer duration of the disease, four years in Koller's case, three years nine months in Mulberger's case, two years three months in Wolfsohn's case, two years four months in Schaffer's case, three years two months in Ostertag's case and three years nine months in the case of Hassin and Parmelee However, in all 6 of these cases the typical Tay-Sachs syndrome was not present for a cherry red spot was not observed Instead the 'equivalent' macular changes previously described were present

To summarize in the early and middle stages of the disease process the diagnosis may be strongly suggested by a history of the development of weakness with gradual loss of muscular power and failing vision in a previously healthy and apparently normal baby particularly if the patient is of Jewish antecedents Subsequent observation may show mental changes and retardation as evidenced by hyperacusis and transient causeless explosive bursts of laughter The presence of a cherry red spot on examination of the fundus is of pathognomonic significance On the other hand, even in the absence of the cherry red spot, the

TABLE XLIX

	Tay Sachs spleen mgm	Normal spleen mgm 24	Tay Sachs kidney mgm	Normal kidney mgm	Tay Sachs liver mgm 27	Normal liver mgm 27
Total cholesterol	3 10	1 8–2 4	2 69	1 4– 8	3 78	2 0– 6
Free cholesterol	1 36	1 6–1 1	0 92	1 0–1 1	0 47	0 4–0 5
Ester chol terol	1 74	0 7–1 3	1 7	0 5–1 /	3 31	1 5–2 2
Total pho pholipids	8 30	5 5–11 0	9 5	7 0–10 0	9 26	9 0–11 0
Sphingomyelin	1 04	0 7–1 0	0 80	0 6–0 8	0 55	0 3–0 5
Cephalin	4 80	1 5–7 0	3 95	2 0–4 0	none	3 0–5 5
Lecithin	2 46	3 0–4 0	4 77	4 0–7 0	8 71	3 0–6 0
Total fatty acids	5 97	4 0–6 2	10 40	5 5–6 2	27 4	8 6–13 0

Through the courtesy of Dr Sidney Farber Pathological Department of the Children s Hospital these organs of a child with Tay Sachs disease were analyzed by Thannhauser Benotti and Reinstein[31] (see above tables) The only difference between the lipid content of normal organs and the brain of a Tay-Sachs child was an increase of the total phospholipids Since participation of the phospholipids did not reveal a rise in the sphingomyelin content of the brain the increased content of total phospholipids is not of significance The analysis of the visceral organs of this case definitely showed that there is no increase of sphingomyelin as in Niemann Pick s disease The conception that Niemann Pick s disease and infantile Tay Sachs disease are two different clinical entities is demonstrated by these analytical findings

E Klenk[1 11 12 13] showed that the gangliosides are increased in the brain of Tay Sachs disease The normal brain contains 0 3 mgm per cent of this substance The amount in the brain of Tay Sachs disease is 4 8 mgm per cent

Since Klenk found the ganglioside content of the brain also slightly increased in Niemann Pick s disease it remains to be seen whether the increase of gangliosides is pathognomonic for Tay Sachs disease or whether an increase may be found also in other heredodegenerative disorders of the central nervous system

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surrounding the nuclei and, according to Ford, are reduced to very fine granules. By using special stains (toluidine blue, thionine and similar stains) it may be seen that the portions of a ganglion cell outside of the nucleus appear clear and empty as though deprived of their contents but that the area around the nucleus stains normally. When stained with hematoxylin and fuchsin the perinuclear space appears empty and colorless whereas the rest of the cell is filled with a granular substance which does not stain with toluidine blue. This granular substance is termed 'prelipoid' and has an affinity for the hematoxylin stains. Chemically it consists of indefinite substances probably related to lipids.

The neurofibrils are intact but are displaced to the periphery of the cell. They show a barred network, the substance of which becomes transformed into numerous vacuoles. These in turn harbor the prelipoid material in the form of fat droplets of varying sizes.

"Associated with the widespread changes in the ganglion cells are the destruction of cortical myelinated fibers (extensive demyelination) and the proliferation of the glia cells, which make the cortex very cellular. No significant changes occur in the blood vessels, and there is no evidence of a cerebral inflammatory process.

In the retina the process is identical with that in the brain. The ganglion cells, which are most numerous in the region of the macular, become swollen and then finally necrotic which causes the retina to appear dirty white or grayish white. The fovea contains no cells and remains transparent, so that the choroidal blood vessels remain visible. As a result there is seen a small red spot the fovea, *surrounded by* an edematous and necrotic zone grayish white in color which is called the cherry red spot. The optic nerves show secondary degeneration."

Chemical findings are shown in Tables XLVI and XLVII.

TABLE XLVIII

	Niemann Pick brain	Tay Sachs brain	Normal brain
	mgm %	mgm %	mgm %
Total cholesterol	6.45	9.90	7.3-15.0
Free cholesterol	5.43	4.10	1.3-4.6
Cholesterol ester	1.02	5.80	6.1-10.3
Total phospholipids	61.0	19.68	25-30
Sphingomyelin	4.84	7.04	4.5-7.0
Cephalin			12-25
Lecithin			4.0-6.0
Total fatty acids			

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lipids, if there is an accumulation of these substances in Hurler Pfaundler's syndrome at all, are bound so firmly to proteins (lipoproteins) that an extraction with the usual fat solvents is not possible Since no analogous situation exists, there seems little likelihood that the substances included in the large vacuolated cells are accumulated lipids or lipid compounds notwithstanding the fact that these cells stain with fat stains Hurler-Pfaundler's syndrome apparently does not originate from an intracellular disturbance of lipid metabolism, nor does it seem to arise from fat infiltration into the cell as a result of hyperlipemia since neutral fat is not increased in the serum, the serum is transparent It becomes more and more apparent from the literature in the last years that Hurler Pfaundler syndrome is a familial bone disease belonging to the group of hereditary osteochondrodystrophies[1 3] The classification of the Hurler-Pfaundler syndrome as familial osteochondrodystrophy does not explain however such features as the enlargement of the liver and spleen as well as the cloudiness of the cornea

Clinical Case

About thirty cases are reported in the literature Ellis Sheldon and Capon[14] review ten cases and reported seven of their own Kressler and Aegerter[9] reviewed the literature up to 1938 and added one new case Since then various roentgenological and histological studies have been reported[3 9 10 12]

The following case history is reported by Kressler and Aegertor[9]

Case LIII — P M male eight and one-half years old was born of healthy unrelated Italian parents Delivery was normal and spontaneous At birth the child seemed normal in every respect The birth weight was eight and one half pounds He was the fifth child four brothers and one sister are living and well He was breast fed until the age of four months when some vague gastrointestinal disturbance necessitated weaning, since that time the child has had intermittent paroxysmal attacks of nausea and vomiting At the age of four and one-half months he developed pneumonia from which he recovered uneventfully A congenital hydrocele was repaired at the age of three months When the child was approximately five months of age the

While this section was in preparation at the publishers Straus Merliss and Reiser[13] reported a case of gargoylism with chemical analysis of the lipids in various organs These authors also did not find any remarkable changes in the fatty content of the organs In their analysis the lymph nodes contained more neutral fat than normal lymph nodes but in the other organs analyzed the lipids were within normal range

parents noticed a peculiar cloudiness of the corneas beginning around the periphery but gradually involving the entire corneal area In the first few years of life this disturbance did not seem to affect the eyesight but later there was definite visual impairment At six months the parents were told the child had rickets

The patient showed definite tardiness in development He did not sit up unsupported until two and one half years nor walk alone until three and one half years the first tooth did not erupt until four years the anterior fontanel closed only between three and one half and four years he did not speak until about the fourth year At the time of his first admission he had a very small vocabulary and enunciated poorly He had never been able to raise his arms above the shoulder level and he walked with a waddling gait

The child was first seen at six and one half years He was short in stature and poorly nourished The musculature was flabby The features were heavy and peculiarly grotesque The scalp hair was fine but the eyebrows were thick and coarse The bridge of the nose was shallow and the nasal passages were filled with a thick purulent discharge The teeth were poorly developed and widely spaced Both corneas were cloudy A 45 degree abduction deformity was evidenced in both shoulder joints together with a 30 degree extension deformity in the elbow joints The wrist and phalangeal joints were normal A mild lumbar kyphosis was present The lungs and cardiovascular system were normal The abdomen was markedly protuberant and a small umbilical hernia was present The liver and spleen were palpable two fingers breadth below the costal cage The genitals were normal Both hip joints showed marked limitation of motion with only 5 degrees of flexion and extension The knee joints showed a 10 degree extension and 45 degree limitation

In the ensuing two years there was a gradual enlargement of the liver and spleen until both were a hand's breadth below the costal cage At the age of seven and one half years he began having paroxysmal attacks of dyspnea with cyanosis and dependent edema Efforts to check this train of events were unsuccessful Roentgenologic examination of the cardiovascular system revealed marked enlargement of all chambers of the heart The patient died of cardiac failure in December 1936 at the age of eight and one half years

The laboratory studies during his last admission were as follows red blood cells 4 59 million white blood cells 7 500 hemoglobin 12 gm normal differential count platelets 90 000 coagulation time 3 min clotting time 2½ min urinalysis normal Wassermann Kline and Kahn tests negative sedimentation index 11 mm blood chemistry blood sugar 91 mgm per cent urea 11 mgm per cent nonprotein nitrogen 4 mgm per cent cholesterol 1 1 to 141 mgm per cent calcium 13 2 mgm per cent phosphorus 5 8 mgm per cent Total protein was 6 14 mgm per cent albumin

"*Skin* shows no changes

'*Dura Mater* On the inner aspect is a layer composed of foamy cells arranged in sheets with a small amount of supporting fibrous tissue and blood vessel

Note on Fat Stains Attempts to stain the lipoid material by stains of the Sudan III type and by the osmic acid and hoyer methods failed'

Chemical analyses appear in Table I

TABLE LI

Chemical Analysis of Organs of Hurler Pfaundler Syndrome (Gargoylism)
(R Holden and S J Thannhauser[9])

Liver	*Gargoylism 6 years old*	*Normal Adult*	*Normal 8 months old*	*Normal 6 year old*
Total fatty acids	7 4	8.6-13.0	7 -8 5	9.0
Neutral fat	4 1	1 - 4 0	3 4-3.9	3 3
Total phospholipids	4 6	9.0-11.0	5 4-6 3	7.8
Saponifiable phospholipids — lecithin and cephalin	4 3	8 -10 5	5 4-6 1	7.8
Sphingomyelin	0 3	0 3- 0 5	0-0.2	0
Total cholesterol	1 2	2 1- 2 6	0.4-0 6	0.4
Free cholesterol	1 1	0.4- 0.6	0 3-0.4	0.4
Cholesterol present as esters	0 1	1 7- 2.0	0 1-0	0
Cerebrosides (normal 0 1-0 5)	0.46			
Spleen				
Total fatty acids	6 3	7.0- 9 0	1 2**	5.0
Neutral fat	7	1 0- 4 0	0.0-0 1	2.8
Total phospholipids	5 1	5 5-11.0	3 1	4 5
Saponifiable phospholipids	4 0	4 8-10.0	3 1	4 1
Sphingomyelin	1 1	0 7- 1 0	0 -0 2	0.4
Total cholesterol	1 8	0 6- 3	0 23	0 6
Free cholesterol	1 7	0 5- 1 1	0 19	0 5
Cholesterol present as esters	0 1	0 - 1 2	0.05	0 1

* Formula of Thannhauser and Reinstein Neutral fat gm percent = gm percent total fatty acids minus (gm percent cholesterol ester X0 72 plus gm percent total phospholipid X0.69) × 1.04

** These figures based on one case age 6 months

These figures demonstrate that neutral fat, cholesterols the phospholipids lecithin and cephalin as well as sphingomyelin are not increased in any of the organs involved in the disease The moderate increase of cerebrosides found solely in the spleen probably is without significance for the pathogenesis of the disease and has to be confirmed by analysis of other cases These analytical findings already corroborated by the analyses of Straus Merliss and Reiser[13] demonstrate that the Hurler Pfaundler sydrome is not a disorder of cellular lipid metabolism or cellular lipid infiltration

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CHAPTER VIII

HEMOCHROMATOSIS

By EDWARD S MILLS

TABLE OF CONTENTS

only 3 cases among 106 000 medical admissions to the Johns Hopkins Hospital. Until 1917 some 75 cases had been reported in the literature. In 1924 the author[13] collected 59 additional cases making the total 134. Ten years later Sheldon[8] accepted 363 published cases. At the Mayo Clinic[9] 30 cases were diagnosed and confirmed by skin biopsy during the 15 years prior to 1938. At the Montreal General Hospital 11 cases were observed during 10 years representing 0.04 per cent of 28 268 medical admissions. The largest reported series is by Boulin of Paris[47] who stated that 70 cases had been observed among 4 266 diabetics attending his metabolic clinic. The disease is said to be relatively common in Africa particularly in association with pellagra[45]

Sex

The male is affected to a much greater extent than the female. The first authentic case in the female was reported by Abbott[3] in 1901. Three additional female cases were reported by the author[13] in 1924. Sheldon[8] found 25 cases in the literature up to 1934 but would accept only 15 of these as authentic. One of the 30 Mayo Clinic cases was a female. The ratio of male to female is thought to be about 20 to 1. In Boulin's series the proportion of female to male was somewhat higher. Beardwood Jr and Rouse Jr[6] reported a single case in the female in 1944

Age

Hemochromatosis is a disease largely of the fifth and sixth decades though the extremes have ranged as far as 17 and 73 years. Nearly half of all cases occur between the 45th and 55th years. Twenty five of the 30 cases reported by Butt and Wilder[9] were in this age period. Fifty six per cent of another series of 70 cases[47] occurred in the fifth decade

Predisposing Causes

In spite of many suggestive studies it must be admitted that the underlying cause of hemochromatosis is unknown. The following theories some of which are based on experimental evidence may be mentioned

Introduction

Synonyms—Bronze diabetes, diabete bronze, visceral hemosiderosis siderogenous hemolysis siderochromatosis, endocrino hepato cardiac syndrome

Definition—A disorder of metabolism characterized by a deposition of iron containing pigments throughout the body, which produce a progressive sclerosis of various organs, notably the liver and spleen The end result clinically is pigmentation of the skin, cirrhosis of the liver, diabetes mellitus, and at times infantilism or congestive heart failure

Historical

While Trosier in 1871 was the first according to Osler,[1] to mention a bronzed cachexia occurring in diabetes, and Quincke[2] in 1880 first called attention to a collection of iron containing pigment in the abdominal organs of a case of diabetes mellitus, the first clinical description of the disease was by Hanot and Chauffard[3] in 1882 Four years later Hanot and Schachmann[4] gave the name diabete bronze and to the associated hepatic cirrhosis cirrhose pigmentaire diabetique under the mistaken assumption that the changes in the liver were secondary to the glycosuria In 1889 von Recklinghausen[5] described the disease under the term hemochromatosis and demonstrated conclusively that the pigmentation of the skin and viscera is due to the deposition in tissues of an iron containing pigment haemosiderin and a non iron reacting pigment, haemofuscin Anschutz[6] in 1899 and Sprunt[7] in 1911 were the next contributors of importance, though largely from the standpoint of compilation Howard and Stevens[8] were the first to report an accurate study of the iron and protein metabolism, which was followed a year later by McClure s paper[9] on the mineral and basal metabolism of the disease Finally Mallory[10] succeeded in producing the disease experimentally in animals and placed the pathology of the disease upon a somewhat more satisfactory footing

Etiology

Incidence

The disease is comparatively rare as shown by Futcher[11] who found

of intrinsic and transfused blood and deposited in an already cirrhotic liver or actually produce the cirrhosis from destruction of the parenchymatous cells of the involved organs Knutsen[69] believes that the disease begins as a primary fibrosis of liver and pancreas causing a derangement of iron metabolism and resulting in hypersideremia The author[49] reported the case of a boy treated for hypoplastic anemia over a period of 11 years by means of blood transfusions He received in all 196 transfusions or 98 liters of blood During this period his skin became a dark bronze color Finally at autopsy liver spleen and other organs were heavily pigmented The pigment present in all tissues was hemosiderosis and yet microscopic examination of the liver failed to show any evidence of Laennec's cirrhosis Such cases suggest that other factors in addition to the presence of pigment must be necessary for the development of the disease Although many authors have studied the deposition of iron administered by various methods none has succeeded in producing all features of the disease[56, 57, 58]

(3) Alloxan Theory—Herbert and his co workers[9, 60] produced necrosis and fibrosis of liver and pancreas with minimal deposition of iron pigment in liver spleen and pancreas and diabetes in 2 of 30 alloxan treated rabbits Their theory of the cause of hemochromatosis is that the cirrhosis of the liver and diabetes are caused by a single noxious agent a ureide the diseased organs then retaining iron abnormally They see little difference between ordinary portal cirrhosis and hemochromatosis other than one of degree added to which is deposition of the iron pigments

(4) Vitamin A Deficiency Theory — Under normal conditions intracellular iron increases with the age of the cell from infancy to early middle life[31] In one sense it is a measure of senility Vitamin A deficiency leads to abnormal absorption of food iron which hastens the time of intracellular iron saturation which in turn leads to destruction of the parenchymatous cells with fibrosis and abnormal iron deposition In support of this theory Taylor Steven and Reid[8] have produced hemosiderosis in cases suffering from vitamin A deficiency by the feeding of iron and Flaum and Stueck Jr[23] reported an extremely low vitamin A content in a case of hemochromatosis

(5) Endocrine Theory — Ledoux and Baufle[84, 85] believe that the underlying cause of the disease is to be found in the pituitary gland They have observed excessive amounts of the thyreo and gonado stimulating factors of the pituitary in the urine of patients with the

(1) *Copper Intoxication Theory* — In 1921 [10] and again in 1931 [46] Mallory reported the experimental production in rabbits and a monkey of a series of lesions similar to those found in the liver in hemochromatosis as a result of adding copper acetate to the food over a period of six months Several authors [50, 51] reported the finding of many times the normal quantity of copper in patients dead from the disease but this abnormality is not confined to pigmentary cirrhosis [9] The author,[11] while in Mallory's laboratory, investigated possible sources of copper intoxication in 19 cases of hemochromatosis but found only 6 had possible contacts with this metal over any long period of time

(2) *Iron Deposition Theory* — The widespread intracellular deposition of iron containing pigments in hemochromatosis has led many authors to explain the etiology of the disease upon this basis Some believe that the iron is derived from extrinsic sources such as food and iron therapy while others favor intrinsic causes such as hemolysis Klechner Jr and his co workers [50] appear to have confirmed Chodos [51] observations that there is increased absorption of iron from the intestine in hemochromatosis These authors, using radioiron (Fe^{59}) have shown increased absorption with abnormally high serum radioiron values compared with suitable controls At the same time the fecal Fe [9] is reduced These experiments suggest that increased absorption of iron from the intestine may be an important etiologic factor in hemochromatosis

Interest in parenteral iron administration as a predisposing factor in hemochromatosis has resulted from the frequent occurrence of generalized hemosiderosis in patients who have received multiple transfusions some of whom have eventually developed hemochromatosis Chesner [5] reported the case of a boy of 14 treated for 6 years for hypochromic anemia with liver and iron At the time of the removal of a hemosiderinized spleen the liver was found to be normal At autopsy some months later there was generalized hemosiderosis and a cirrhotic liver The liver contained 47 gms of iron though only 2 75 gm had been given by transfusions

Rosenthal [53] suggested that the fundamental disturbance was the inability of the liver to change ferric iron to ferrous Smith and Gault[5] believe that hemochromatosis is analogous to von Gierke's disease the iron entering the cell in the normal way after which it is transformed into an insoluble form incapable of excretion The occurrence of cases of the disease in association with aplastic anemia [44] has led to the belief that the excesses of intracellular iron are derived from the destruction

color except for small pale areas which represent islands of regenerated liver cells Histologically the pigment is seen to be more abundant at the periphery of the lobule The spleen usually is enlarged and firm but may be of normal size It is brownish red in color due to pigment in the phagocytes of the pulp Moderate fibrosis usually is present There is also some chronic passive congestion consequent to the hepatic cirrhosis

The pancreas also has a rusty color somewhat paler than the liver Grossly it is either a small atrophic organ or an enlarged fibrous gland infiltrated with fat The pigmentation and fibrosis involves both acinous and islet cells The adrenals show pigmentation of the outer layer of the cortex but otherwise are intact The glands of the stomach and intestine particularly the jejunum and duodenum are somewhat pigmented especially at their bases In the heart the pigment is abundant around the nucleus of the muscle fibers thus causing death of the fiber and fibrosis

Pigmentation and sclerotic changes occur to a lesser extent in almost every organ and tissue of the body including the lymph nodes salivary glands thyroid the brain the hypophysis and even the tracheal cartilages The lymph nodes adjacent to the pancreas are notably chocolate in color and heavily pigmented The amount of heavy metals in various organs may be great Iron content of liver pancreas and salivary glands may be 50 to 100 times the normal It may be four times the normal in striated muscle The iron and copper content of the liver and spleen in hemo chromatosis is given by Flaum and Stueck Jr [33] as follows

	Liver		*Spleen*	
	Iron	*Copper*	*Iron*	*Copper*
Flaum and Stueck s case	33	6 5	0 56	8 3
Other cases	3 6–2 1	4–40	0 27–0 13	10–4
Normal	0 05	2 5	0 14	2 7

All values are given in grams per 100 grams of dried substance

It is thus evident that both iron and copper content of these organs is increased but the iron to a greater extent than the copper Sprunt [7] found 38 7 grams of iron in the liver of one of his cases while Hensel [29] reported 33 92 grams from another In Hensel s case the bile contained 37 mgm per 100 c c indicating excretion of pigment by this route Sheldon [30] reports an increase in the calcium content of the liver and pancreas in this disease which he ascribed to parathyroid involvement although no actual increase in blood calcium has been reported

hemochromatosis syndrome and, therefore, suggest that dysfunction of the hypophysis may be the primary cause of the disease They point to Garnat and Caroli's case of hemochromatosis which presented clinically the acromegaly syndrome and at necropsy hypertrophy of the hypophysis due to eosinophilic cell hyperplasia

Morbid Anatomy

First and foremost in importance in the morbid anatomy of hemochromatosis is the deposition of pigments in the skin and parenchymatous organs It is believed that the sclerotic lesions in liver, pancreas, and other organs are due directly to the irritation from these two pigments hemofuscin and hemosiderin It is by no means certain, as Mallory has suggested that hemofuscin is a precursor of hemosiderin Hemofuscin is an iron free black pigment containing 3 7 per cent sulphur, found primarily in smooth muscle and is, according to Gillman,[63] a cytolipochrome It is abundant in arteries the gut particularly the jejunum and duodenum the genitals the connective tissues and heart muscle

Hemosiderin on the other hand contains 55 per cent iron It is abundant in the gland cells of the various parenchymatous organs as liver pancreas lymph nodes, kidneys, parathyroid thyroid and suprarenal glands and even in the male breast It may be found in the anterior pituitary gland but the posterior lobe escapes Striated muscle may be affected although smooth muscle invariably is free

In the skin three types of pigment may be found the hemofuscin in the connective tissues and the hemosiderin in and about the sweat glands and in the corium Pigment in the epidermis usually is melanin due probably to hemosiderosis of the suprarenal The pathological lesions other than pigmentation found in this disease are mainly degenerative and sclerotic pigmentation causing degeneration followed by fibrosis

The cirrhosis of the liver which is an outstanding feature resembles in many ways that seen in alcoholic cirrhosis except for the rusty to dark brown color The organ as a rule is finely nodular and tends to be larger than in the corresponding stage of alcoholic cirrhosis due to more active regeneration of liver cells which can be recognized easily because they contain less pigment It is rarely complicated by fatty infiltration The cut surface of the organ presents the same brown

potence 1. per cent of which had definite testicular atrophy Thirty-four per cent of the cases showed loss of pubic and axillary hair

Physical Examination

The appearance of the patient on physical examination often is striking The normal skin pigmentation is intensified particularly in the skin folds and about the genitalia and nipples Over the forehead the face the backs of the hands wrists forearms and the lower extremities pigmentation characteristic of the disease is found It occurs as patchy grayish brown areas irregular in outline and distribution as if the parts were covered with patches of dirt The general nutrition is as a rule poor in contrast to the fullness of the abdomen The liver invariably is enlarged and may reach to the level of the umbilicus Its surface is firm but the pebble leather or hobnail surface is felt with difficulty unless the abdominal wall is thin A small or normal sized liver usually means that shrinkage of a previously enlarged organ has taken place and then ascites and jaundice are common Whenever the liver is unusually large and especially if the enlargement is not uniform primary carcinoma of the liver should be suspected [13]

The spleen is palpable in only about half of the cases The heart may be enlarged Seven of the 30 Mayo Clinic cases had cardiac enlargement Both Bork [15] and Blumer and Nesbit [14] found a heavy deposition of hemosiderin in the heart muscle in their reported cases together with extensive fibrosis suggesting cause and effect but other authors although admitting the frequency of myocardial hemosiderosis deny that fibrosis commonly results

Laboratory Findings

Urine — The urine as a rule contains increased amounts of urobilinogen as well as glucose Cylindroids bearing hemosiderin have been demonstrated in the urine by Sprunt Marsh [1] and others The demonstration of hemosiderin in the urinary sediment is perhaps best carried out by the method of Rous [8] which involves mixing of the sediment with blood serum and fixing it on a slide after which it is treated with strong ammonium sulphide then stained by potassium ferrocyanide and hydrochloric acid By this technique hemosiderin is demonstrable as large blue crystals

Symptomatology

The symptoms of hemochromatosis are, as a rule, referable to the cirrhosis of the liver, the pigmentation of the skin or the diabetes In the series of 30 cases diagnosed during life at the Mayo Clinic the presenting symptoms were referable to the skin pigmentation or the enlarged liver in 27 Symptoms of diabetes were present in only 9 although 24 of the cases showed glycosuria A review of 65 proven cases with clinical data published by various authors since 1911 shows (1) 40 sought treatment for symptoms referable to an hepatic cirrhosis as pain in the region of the liver, swelling of the abdomen hematemesis or dyspepsia Twenty-three of these had an associated latent glycosuria Only 10 had ascites, and jaundice was rarely a feature (2) In 13 cases the presenting symptoms were referable to the diabetes weakness loss of weight, polydypsia, or polyuria Six were admitted in diabetic coma or precoma In all of these cases hepatic cirrhosis was present but latent, though the history usually revealed some symptoms referable to it (3) In only 6 cases was pigmentation of the skin a presenting symptom, although it was invariably present In the Mayo Clinic series the chief symptoms of the 30 cases on admission were asthenia 10 cases symptoms of diabetes 9 dyspnea 4 ascites 3, neuritis 2 abdominal pain 2 impotence 2 poor vision 1 edema 1 and diarrhea 1

It is thus evident that the great majority of the patients with the disease seek medical advice because of symptoms referable to the cirrhosis of the liver and only about one in five comes because of diabetes although glycosuria and pigmentation of the skin usually are present at the time

Endocrine Cardiac Syndrome -- In France particularly attention has been drawn to the frequency of cardiac decompensation and endocrine changes in hemochromatosis[39, 40, 41, 63, 64, 47] These cases frequently show as presenting symptoms the features of congestive failure with evidence of endocrine dysfunction usually loss of secondary sex characteristics and impotence due to testicular atrophy The Addison syndrome is rare[63, 47] Oswald[61] and later Stoder[49] reported the case of a 17 year-old boy who died of heart failure following auriculo ventricular block His genitals were infantile and there were no secondary sex characteristics Autopsy showed pigmentary cirrhosis of the liver generalized hemosiderosis with fibrosis, and siderosis of the heart muscle Boulin s series of 70 cases included 28 instances of im

potence 12 per cent of which had definite testicular atrophy Thirty four per cent of the cases showed loss of pubic and axillary hair

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Blood—The blood picture is not especially characteristic of the disease In common with other types of cirrhosis cases may show moderate hyperchromic anemia with granulocytopenia Still other cases show only slight hypochromic anemia The average blood count in 30 cases was 399 million red blood cells, 6,500 white blood cells and 74 7 per cent hemoglobin Smears were normal in 15 of 18 cases On the other hand Marl off[4] has reported 1 case, in which the disease at first simulated pernicious anemia although satisfactory response to liver extract injections was not obtained Terminally hemorrhagic features and grave hyperchromic anemia supervened, and this was the cause of death At autopsy the bone marrow was megaloblastic This author believed that the ultimate failure of liver therapy was due to reticulo endothelial block by hemosiderin In this connection it must be pointed out that there is a syndrome of generalized hemosiderosis with necrosis and fibrosis of the liver which occurs in certain cases of aplastic anemia and this may be readily confused with true cases of hemo chromatosis In fact Zeltmacher and Bevans [4] state that aplastic anemia due to toxins leads to cirrhosis of the liver and this with the deposited iron from intrinsic and extrinsic sources produces a picture indistinguishable from hemochromatosis It should be pointed out however that such cases though clinically suggestive of hemochroma tosis do not show the hemofuscin in the tissues a fact readily demon strable by skin biopsy in most instances Generalized hemosiderosis with intense skin pigmentation occurred in a case of hypoplastic anemia of 12 years duration reported by the author, [4] but the liver showed no cirrhosis The hemosiderosis was considered to be due in part to 196 transfusions which he received during the course of his long illness Similar cases have been reported by other authors They tend to min imize the importance of the deposition of hemosiderin as a fundamental factor in the etiology of the disease

Liver Function—The present unsatisfactory status of liver function tests necessitates a compilation of the results of many tests in order to arrive at a reasonably accurate idea of the function of the liver Among these are plasma bilirubin urine urobilinogen plasma protein estimation prothrombin time bromsulphalein excretion cephalin flocculation Takata-Ara and thymol turbidity tests It should be remembered that none of these tests is ideal and probably will not measure anything less than a 60 per cent reduction in functioning liver tissue Liver puncture offers a means of fairly accurate estimation of the condition of the liver

in hemochromatosis since the process is generalized throughout the organ but the procedure is not without risk especially in the presence of jaundice or a prolonged prothrombin time

Electrocardiograph—Electrocardiographic changes indicating myocardial damage or interference with conduction have been reported frequently in the disease Only one in 6 of Boulin s 70 cases had a normal electrocardiogram Low voltage left axis deviation and inversion of T in one or more leads were the common findings Petit[61] reported a case showing complete auriculoventricular block with low voltage and abnormal T deflections He collected 25 similar case records from the literature Prolongation of the P R interval has been reported by a number of authors[1 43 64]

Skin Tests—In addition to skin biopsy which will demonstrate the characteristic pigments the presence of iron pigment in the skin may be demonstrated by Fishback s test[63 71] The test is carried out as follows Inject intradermally at a site of pigmentation one tenth of a cubic centimeter of equal parts of 0 5 per cent potassium ferrocyanide and one hundredth normal hydrochloric acid A blue color appears at *once at the site of injection gradually darkening for about an hour* The color lasts for two weeks According to Fishback the test is specific for hemosiderin deposition in the skin

Complications

One of the most frequent complications of hemochromatosis is primary carcinoma of the liver[87 88] Oshlag Martin and Binford[86] who reported a recent case were able to collect 37 other cases from the literature It occurred 3 times in the author s series of 17 cases[13] Sheldon found 26 in 363 accepted cases of hemochromatosis an incidence of 7 1 per cent according to Stewart[37] Warren and Drake[49] in comparing their experience with other authors found a much higher incidence of carcinoma of the liver—30 per cent or 6 cases of malignancy in 20 cases of hemochromatosis Reviewing the occurrence of primary carcinoma of the liver in Laennec s cirrhosis they found an incidence of 4 4 per cent in 2 114 cases The combined experience of a number of authors would place the incidence of primary carcinoma at 18 9 per cent nearly five times as common as in portal cirrhosis of the Laennec type These comparative figures seem to point to the importance of iron pigments in predisposing malignant hepatoma even though they assume

a less certain role in the production of the cirrhosis

An unusual complication has been reported by Herzenberg[1] from the Jansa Clinic of Moscow She described 3 cases with cerebral hemorrhage shown histologically to be caused by weakening of the arterial wall as a result of hemosiderin and hemofuscin deposition Knutsen[23] reported generalized osteoporosis with fractures of 2 dorsal vertebrae in a well-developed case The serum calcium and phosphorus were normal Two similar cases have been recorded in the literature[8]

Diabetic coma is less frequently a terminal event in the disease since the introduction of insulin but still occurs in progressive and insulin resistant cases Tuberculosis of the lungs and peritoneum acute parotitis acute otitis media, and septicemia are rare complications Death due to mucormycosis infection of the meninges was reported in one case[0]

Diagnosis

The triad of clinical signs, pigmentation of the skin hepatic cirrhosis and glycosuria, is pathognomonic and we believe justifies an absolute diagnosis, provided the pigmentation of the skin is due in part at least to hemosiderin or hemofuscin Addison s disease and argyria in the exceptional case or in the very early stage of the disease may offer some difficulty Excision of a portion of skin from the pigmented areas should always be carried out Granules of hemosiderin free in the urinary sediment or in the desquamated renal epithelial cells, have been demonstrated frequently by the method of Rous[36] These may occur also in hemolytic jaundice and pernicious anemia but both these diseases are readily differentiated from hemochromatosis

The greatest difficulty in the diagnosis of the disease lies in the fact that many cases are seen before the clinical triad can be detected The patient s presenting symptoms may be those of congestive failure and the enlarged liver *considered to be due to passive congestion* The absence of hepatic tenderness and particularly the presence of splenic enlargement should suggest the true underlying cause particularly if associated with diminished sugar tolerance or skin pigmentation In other instances the diabetes and skin pigmentation may occur without clinical evidence of hepatic cirrhosis In such cases if the laboratory signs are suggestive of hepatic cirrhosis a skin biopsy or liver puncture often will confirm the diagnosis

Prognosis

The prognosis in hemochromatosis is grave Patients are subject to the same hazards as occur in other forms of portal cirrhosis with the additional risk of death in diabetic coma Hepatic decompensation with resulting coma or massive gastro intestinal hemorrhage account for many deaths Until treatment by phlebotomy was instituted within the last decade no therapy was known to arrest the process of iron deposition and portal cirrhosis It is as yet too soon to state that this method of therapy will arrest the process but several authors[75, 76] have reported encouraging results in selected cases

To other hazards must be added the risk of primary malignant hepatoma[77] When the stage of glycosuria has been reached the expectancy of life is usually though not always relatively short Butt and Wilder[9] in their series of 30 cases found that the diabetes usually was mild and controlled frequently by diet alone or diet combined with insulin in small doses Only an occasional insulin resistant case was encountered In spite of this 13 of their cases died within a relatively short period of the time after the diagnosis was made Two cases lived 9 years one 8 one 7 and one 13 years On the other hand cases reported by Mallory[4] and Rushton[43] showed progressive intractible diabetes uncontrolled by insulin Coma in one of Petit s cases was easily controlled by insulin whereas Werner s[7] case was uncontrolled by 100 units per day Boulin lists the prognosis as follows (1) after the development of diabetes expectancy of life is 1 to 8 years with an average of four (2) after symptoms and signs of hepatic cirrhosis 3 to 17 years with an average of 7 (3) after pigmentation of the skin 3 to 46 years with an average of 8 years

In a few cases notably that of Althausen and Kerr[17] the control of the diabetes resulted in partial clearing up of skin pigmentation in a period of 3½ months On the other hand a case under diabetic control in the outpatient department of the Montreal General Hospital failed to show any change in the skin pigmentation after four years of treatment

Treatment

Until the cause of hemochromatosis is better understood prevention of the disease must be largely speculative The similarity of the pathologic process in the liver to that in Laennec s cirrhosis suggests that a

a less certain role in the production of the cirrhosis

An unusual complication has been reported by Herzenberg [4] from the Jansa Clinic of Moscow. She described 3 cases with cerebral hemorrhage shown histologically to be caused by weakening of the arterial wall as a result of hemosiderin and hemofuscin deposition. Knutsen[79] reported generalized osteoporosis with fractures of 2 dorsal vertebrae in a well developed case. The serum calcium and phosphorus were normal. Two similar cases have been recorded in the literature.[8]

Diabetic coma is less frequently a terminal event in the disease since the introduction of insulin but still occurs in progressive and insulin resistant cases. Tuberculosis of the lungs and peritoneum, acute parotitis, acute otitis media, and septicemia are rare complications. Death due to mucormycosis infection of the meninges was reported in one case.[70]

Diagnosis

The triad of clinical signs, pigmentation of the skin, hepatic cirrhosis and glycosuria, is pathognomonic and we believe justifies an absolute diagnosis, provided the pigmentation of the skin is due in part at least to hemosiderin or hemofuscin. Addison's disease and argyria in the exceptional case or in the very early stage of the disease may offer some difficulty. Excision of a portion of skin from the pigmented areas should always be carried out. Granules of hemosiderin, free in the urinary sediment or in the desquamated renal epithelial cells, have been demonstrated frequently by the method of Rous.[36] These may occur also in hemolytic jaundice and pernicious anemia, but both these diseases are readily differentiated from hemochromatosis.

The greatest difficulty in the diagnosis of the disease lies in the fact that many cases are seen before the clinical triad can be detected. The patient's presenting symptoms may be those of congestive failure and the enlarged liver considered to be due to passive congestion. The absence of hepatic tenderness and particularly the presence of splenic enlargement should suggest the true underlying cause, particularly if associated with diminished sugar tolerance or skin pigmentation. In other instances the diabetes and skin pigmentation may occur without clinical evidence of hepatic cirrhosis. In such cases, if the laboratory signs are suggestive of hepatic cirrhosis, a skin biopsy or liver puncture often will confirm the diagnosis.

Another problem which has been encountered in phlebotomy therapy of hemochromatosis is the effect of the venesection on iron absorption from the gut By radio iron studies Chodos and his co workers[79] have shown that hemochromatosis patients undergoing phlebotomy therapy absorb a great deal more iron of both food and inorganic varieties than those not on this treatment This fact points to the necessity of frequent and long continued withdrawal of blood which might in time exhaust the bone marrow if not the courage of the patient

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diet high in protein and the sparing use of alcohol should be recommended. Mallory's view that excessive intake of copper salts played an important role in the etiology of the disease has not been supported by subsequent investigations.

The management of the disease, when fully established, consists in the symptomatic treatment of the cirrhosis and the control of the diabetes. As already intimated, the latter may be accomplished by dietetic means or insulin may be required as well. The severity of the diabetes cannot be predicted from the degree of hepatic cirrhosis or skin pigmentation. Where insulin is required, special care is demanded to prevent insulin shock, as the ability of the liver to manufacture and store glycogen appears to be defective. This warning is particularly applicable to the forms of insulin having prolonged action such as the protamine zinc variety. Acidosis is common and insulin reactions are frequent even during stages of acidosis and moderate hyperglycemia. Instances of glycosuria in hemochromatosis easily controlled by insulin have been reported by a number of authors[6, 61, 66, 69].

Wishinsky[80] has given Ethelenediaminetetraacetic acid intravenously to mobilize and remove iron in one case of hemochromatosis. This chelating agent is said to form a water soluble compound with iron which is not ionized and readily excreted by the kidney. Unfortunately the amount of iron so removed is too small to be of much therapeutic value in this disease and reduction in prothrombin activity has been observed.

The treatment of hemochromatosis by frequent venesection—the latest contribution to the therapeutic armamentarium—is encouraging though still on trial. A half liter of blood is removed by venesection on an average of once a week. Sometimes the plasma is replaced—more often not. In from one to three years the patients have noted a decrease in the severity of the diabetes—a reduction in the skin pigmentation and iron in the bone marrow with an improvement in the function of the liver. Patients so treated have resumed useful lives after long periods of invalidism. Davis Jr. and Arrowsmith[75] have collected 15 patients so treated with improvement in 12. It is of some interest that these authors found only six of their 10 patients suitable for therapy and only 3 showed continued improvement. For the success of therapy the bone marrow must be sufficiently active to compensate for the blood removed. Increasing anemia has necessitated discontinuance of therapy in some cases. Warthin's case[78] showed striking improvement.

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CHAPTER IX

OCHRONOSIS

By EDWARD S MILLS

TABLE OF CONTENTS

INTRODUCTION

Definition — A rare disorder of metabolism associated with blacken ing of the cartilages and fibrou tissues pigmentation of the skin osteo arthritis and the presence of dark urine due to alkapton melanin or to derivatives of carbolic acid (Osler)

and 41 in the female The sex of one case was not given There is a slightly higher incidence of males in the alkaptonuric group and of females in the carbolochronotic series It is essentially a disease of middle life Of 64 cases in the carbol and alkaptonuric groups the greatest incidence was in the sixth decade (1 cases) At least 47 occurred in the fifth sixth or seventh decade of life The youngest cases are males of 23 and 21 years reported by Poulson[1] in 1910 and Martin[34] in 1955 and the oldest a woman of 88 reported by Swirsky [9] in 1944

Heredity —Heredity plays some role in the alkaptonuric group as illustrated by Osler s 2 patients who were brothers and Kolaczek s 3 sisters offspring of a consanguineous marriage

One of Smith s [6] patients also illustrates the effect of heredity This patient s parents were first cousins Three brothers showed alkaptonuria and at least one of these had ochronosis Three of 4 daughters were alkaptonuric, and 2 of these showed premature calcification of the costal cartilages One grandson had alkaptonuria Smith believes that this is the first family pedigree in which the disease is expressed as a dominant instead of a rare recessive Mendelian characteristic although Uebermuth s[33] patient had 5 alkaptonuric grandchildren and an alkaptonuric nephew On the other hand Seaborn s case [3] was the tenth of 13 children none of whom had the anomaly Furthermore Seaborn was able to examine 135 descendants in direct line 5 in the first generation 26 in the second 8 in the third and 2- in the fourth generation without finding any cases of the disease In rare instances there is a history of alkaptonuria from birth as in the cases reported by Seaborn[2] Bhatia and Soderbergh[11] though the ochronosis did not become evident till late in life Abbott Jr Mandeville and Rein[30] who reported alkaptonuric Negro children of 15 and 10 years plan to report later whether ochronosis develops

Morbid Anatomy

Pigmentation —The striking feature is the pigmentation of the cartilage of the ears of the various joints of the ribs intervertebral discs synchrondroses of the pelvis and of the trachea as well as the tendinous filaments of the heart the cardiac papillary muscles normal and diseased heart valves the cerebral and spinal dura mater and in some cases the skin the intima of the blood vessels the kidney parenchyma and even

Historical Note—Virchow[1] in 1866 first described the disease from the postmortem room and named it 'ochronosis' (Greek (ωχρός) pale yellow (νόσος) disease) on account of the pale yellow color of the pigment granules under the microscope. In 1902 Albrecht suggested its association with alkaptonuria. Osler[3] in 1904 was the first to make a diagnosis of the condition intra vitam. Ludwig Pick[4] in 1906 contributed greatly to our knowledge of its chemistry and pathogenesis. One year later Gross and Allard[5] drew attention to the commonly associated deforming arthritis and suggested that these changes were due to irritation caused by the deposited pigment.

Etiology

Incidence—The disease is seldom encountered. In 192- Oppenheimer and Kline[6] collected 41 cases of the disease. During the next two decades cases were reported from Germany[18, 19], from England[0, 21], from India[2], from Italy[3], from Austria[4], from Canada[5], and from the United States[6], bringing the total to 78. In 1944 and 1945 three additional cases were reported[8, 9, 7] a total of 81 cases. Martin[34], reporting 12 cases of alkaptonuria from the Mayo Clinic files in 1955, states that there have been 200 cases recorded during the last 370 years. Eight of the 12 cases had ochronosis.

Segregating the 93 cases according to the nature of the pigment found in the urine, an endogenous group, in which the pigment is alkapton or rarely melanin, and an exogenous group, in which the pigment is phenol or one of its derivatives, the results are as follows:

Ochronosis with alkaptonuria	55 cases
Ochronosis with alkaptonuria and melanuria	1 case
Ochronosis with melanuria	2 cases
Carbolochronosis	21 cases
Ochronosis with undetermined pigment	14 cases

In 2 cases of alkaptonuria reported by Abbott, Jr, Mandeville and Rein[0] the other features of the disease were lacking so these are not included. In recent years carbolochronosis has all but disappeared due to the fact that phenol and its derivatives are seldom employed in therapy.

Sex and Age—In the endogenous group the alkaptonuria is invariably present from birth[35] although the other clinical features of the disease do not develop for some time as the figures below indicate. The cases are divided almost equally between the two sexes, 47 in the male



Fig 1 Ochronotic Spine
Courtesy of Dr M Goldston

the lymph nodes In none of the reported cases has there been an opportunity of sectioning the ochronotic eye

Bone Changes—In a great majority of fully developed cases of ochronosis arthritic changes occur These are of two types, and they involve mainly the spine, the pelvis the shoulders, knee joints, and the costal cartilages The one type resembles closely the hypertrophic or osteoarthritis of advancing years, the other is characteristic of ochronosis and is a fairly generalized calcification of cartilage The costal cartilages may become completely calcified even at an early age, the intervertebral discs also becoming completely calcified Calcification may also occur in the spinal ligaments Puhr[8] reported a case in which bony changes were extreme and resembled osteomalacia Figure 1 is an X-ray photograph of an ochronotic spine through the courtesy of Dr Goldston[3]

Other Degenerative Changes—Cardiovascular degenerative changes are common and atheromatous placques in the endocardium or the intima of the vessels frequently are deeply pigmented

Nature of the Pigment—The nature of the ochronotic pigment is unknown It is gray brown or black in color to the naked eye, according to the situation and amount Microscopically, as Virchow pointed out the granules are of a pale yellow or ochre color They occur in the ground substance of cartilage in the skin, where they are found in the connective tissue bundles of the corium, pars reticularis and papillaris and in atheromatous placques The pigment usually has a rather homogeneous appearance as in the matrix of cartilage but may be definitely granular especially where it occurs within cells as in the kidneys The distribution in the skin is in contrast to that in Addison s disease where it is found in the deeper layers of the rete malpighii It is not a hematin derivative as Virchow suggested, but belongs to the group of so called melanins being similar to the pigment of brown atrophy Janney's microchemical analysis of pigment from the urine and from the tissues *in a case reported by Oppenheimer and Kline*[6] *showed that the* pigment definitely belonged to this group Professor Schmolfuss who analyzed the pigment in Gonnermann s case[10] also came to the conclusion that it was a melanin On the other hand the pigment in Puhr s[8] case, studied microchemically by him and gravimetrically by Professor Hari belonged neither to the melanin nor the hematin groups He showed that it was not akin to the lipochromes In short he was unable to classify it Likewise Peat made an exhaustive biochemical study of the pigment of



Fig 1 Ochronotic Spine
Courtesy of Dr M Goldston

the urine in the exogenous case reported by Berry and Peat[1] without demonstrating its nature although on one occasion they found hydroquinone From their studies Berry and Peat believe that the formation of the pigment in the urine is an oxidative process with an optimum pH of 9 - It well may be that the pigment is not identical in all cases and this view is supported by the finding of clinically different pigments in the urine

Complications—Tuberculosis has been described as an associated condition[14] Young[?7] reported a case of prostatic lithiasis ochronotica and found 6 others recorded in the literature of the disease Chemical analysis of the calculus showed calcium phosphate and oxalate permeated by black pigment which he was unable to identify

PATHOGENESIS

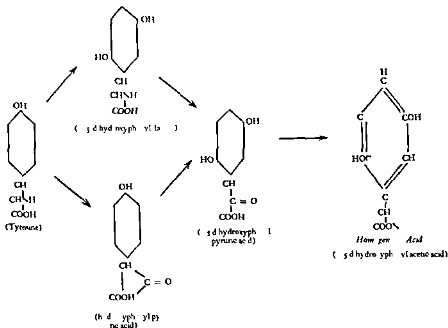
Virchow s hematogenous theory which regarded ochronosis as a peculiar form of hemochromatosis, is now abandoned Attempts to produce the disease experimentally have failed Gross[9] tried unsuccessfully to produce it in dogs and a calf by chronic poisoning with phenol He also placed cartilage in a solution of homogentisic acid and found that it quickly became discolored, in a month resembling the cartilage in ochronosis He further suggested that there may be some substance in normal blood which destroys homogentisic acid lacking in patients who have alkaptonuria or ochronosis This is in line with Albrecht s view that homogentisic acid or one of its derivatives combined with the chondromucoid or the chondroitin sulphuric acid of the cartilage to form the pigment These theories do not account for the group of cases associated with the use of phenol in which alkaptonuria has not been demonstrated

The most plausible explanation of the mode of production of the pigments in the disease is by Pick[4] He suggested that through the action of the oxidative ferment tyrosinase, the phenol substances in exogenous group and the homogentisic acid molecule in the endogenous group are changed into melanin pigment which is deposited in the tissues Further, Abderhalden and Guggenheim[10] have shown by their chemical studies that it may be presumed that an accumulation in the human organism of excessive and abnormal amounts of substances possessing the oxy phenyl group leads to the production of melanin pigments by ferment action Both types of cases contain this chemical entity In obscure

cases, such as Puhr's[8] it seems not unlikely that the pigment may be of very complex constitution its tyrosin molecule supplying the necessary oxyphenyl group In spite of the purely theoretical nature of the ferment tyrosinase this explanation is the most satisfactory one at present

The observation of Swirsky [9] that normal individuals convert tyrosine and phenylalanine to homogentisic acid and then into carbon dioxide and water whereas in the ochronotic individual these two amino acids are excreted as homogentisic acid throws light upon the origin of this abnormal substance in the urine but it does not explain the nature of the pigment within the body It is of interest that this author found that from 40 to 50 per cent of the total nitrogen in the urine in the ochronotic may be derived from this source

According to Swirsky [9] the normal oxidation of tyrosine is shown in the accompanying formula Normally at this level of oxidation the benzidene ring opens in such a way as to form acetoacetic acid which in turn breaks down into CO_2 and H_2O In the ochronotic individual the process stops at the homogentisic acid level and is excreted in the urine as such



Symptomatology

The triad of symptoms pigmentation of the sclerotics and ears (Fig 2) the dark color of the urine and the arthritis is pathognomonic

Pigmentation—Pigmentation is the characteristic feature and the one common to all cases The staining, as already mentioned is very widely diffused involving all fibrocartilaginous structures the eye the external cartilages the tendons, and the skin Smith[6] found that with

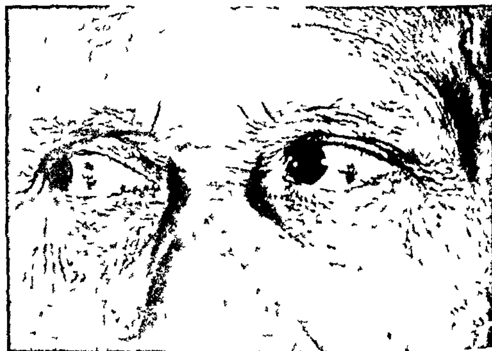


Fig Ochronotic pigment in sclerae
Courtesy of Dr M Goldston

one exception ocular pigmentation has been reported in every proven case since 1910 The scleral pigmentation (Fig 2) is readily differentiated from that seen in Addison s disease and from arsenic melanosis by its superficial localization in the palpebral fissures temporally and nasally It is either a diffuse gray color or more commonly semilinear or V-shaped situated midway between the margin of the cornea and the outer or inner canthus The color varies from a deep brown

to a jet black Scleral melanosis is not so situated (Fig 1) Corneal involvement frequently occurs and it is characteristic By retro illumination discrete brown pigment spots are visible in the superficial layers near the temporal and nasal limbi They appear like oil droplets on water and according to Smith[6] cannot be confused with any other slit lamp biomicroscopic finding By this same method of examination brown pigment is visible in the conjunctiva subepithelial in position located near the borders of the scleral spots and deposited in crescent spiral or open ring formations Smith s article contains excellent color illustrations of these changes in the eye

The pigmentation of the eye should not be confused with the pigment occurring in melanotic sarcoma At least one instance is recorded in which an ochronotic eye was enucleated because it was thought that the discoloration was due to malignancy of this type This case which was reported by Slinsnes[39] had arthritis and discoloration of the body cartilages characteristic of ochronosis The diagnosis was confirmed at autopsy

The pigmentation of the cartilages though widespread is obviously visible only in certain situations such as the ear the nose and possibly the eyelids and larynx In the ear it appears blue black steel blue or leaden color very like that produced by dilated veins and is deepest in the concha extending along the antihelix The pigment is opaque to light and can be brought out strikingly by transillumination such as placing a flashlight behind the lobe of the ear The staining of the fibrous tissues and the tendons is seen best about the knuckles the knees and the tendons of the feet In these sites usually it is of a steel gray color The toenails have been affected in two cases In one case pigmentation which was intense was limited to the 5th 6th and 7th costal cartilages[11]

The skin of the face has been involved in at least 13 cases in some of which the pigmentation was described as coffee colored The face of one of Berry s cases was a uniform yellow brown color with butterfly wing intensification over the cheeks In one of Osler s cases there was distribution of pigment over the nose and cheeks like that of lupus erythematosus of coal black color suggesting a dense collection of comedones Bhatia s case had numerous small cutaneous hemorrhages in addition to pigment some of these ulcerated In other cases the color of the skin has been described as a pure melanosis just as if a patch of the blackest negro skin had been inserted Poulsen[1] has noted a staining of the sweat from the axilla indicating that the pigment may be

Symptomatology

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Fig 2 Ochronotic pigment in sclerae
Courtesy of Dr M Goldston

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Other tests which have been reported are

(1) The darkening of the urine by absorption of oxygen from the air is greatly hastened by the addition of an alkali such as potassium hydrate

(2) Upon heating with Fehling s solution a deep brown color develops and a copious reduction occurs It is important to remember that alkaptonuria is a reducing substance—a fact which may lead to the mistaken diagnosis of diabetes mellitus as appeared to be the case in at least one instance[18]

(3) An ammoniacal solution of silver nitrate is reduced quickly by it in the cold

(4) When heated with Hylander s solution a darkening occurs due to the action of the alkaline reagent upon the urine but no black precipitate forms from reduction of the bismuth salts

(5) When a dilute solution of ferric chloride is added to the urine drop by drop a deep blue color appears for a moment as each drop falls and continues until oxidation is complete

(6) The polariscopic and fermentation tests for glucose are negative

It must be borne in mind of course that alkaptonuria may be inter mittent or even absent for years at a time

In 21 of the reported cases the darkening of the urine was associated with the presence of phenol or one of its derivatives as a result of the prolonged use of phenol picric acid or other phenol compounds as external applications The carboluria disappears gradually after the withdrawal of the poison In Berry and Peat s [1] case a woman who had used dressings of 5 per cent phenol on leg ulcers over a period of 35 years the urine was free from phenol 5 days after the dressings were discontinued It is of interest that reapplication of the dressings for 21 days resulted in carboluria beginning the fifth day but no pigment appeared nor did the urine darken at all on standing The authors there fore feel that it is not the phenol or one of its derivatives per se which causes the dark urine but rather that these substances cause an oxidative process resulting in pigment formation They were unable to isolate the pigment although they recovered a hydroquinone on one occasion The addition of this substance to normal urine gave a color similar to that recognized in the patient s urine

In at least 2 cases of ochronosis the urinary pigment has been dem onstrated to be melanin This pigment is decolorized by (1) potassium permanganate sodium sulphite oxalic acid solution (2) bichromate

excreted by the sudoriferous and ceruminous glands Sugar and Waddell[37] have reported 10 cases of pigmentation of the skin nail beds cartilages of ribs, nose, ears and simulating ochronosis due to prolonged use of atabrine He was unable to determine the nature of the pigmentation but in no instance were all aptons present in the urine—an important differential point

Young [7] found 7 instances in which the pigment was visible in prostatic calculi

Urinary Changes—As already recorded the dark brown urine, noted at the time of voiding or after exposure to air for a short time is in a majority of cases due to the alkapton homogentisic acid In only 2 of the 83 reported cases was the urinary pigment proved to be melanin alone In one case both pigments were present The metabolic abnormality which causes alkaptonuria is frequently present at birth and has been known to be present for at least 30 years before clinical evidence of the disease in its classical form Furthermore, not all cases showing alkaptonuria have developed the other chemical signs The cases reported by Seaborn and by Bhatia were known to have had alkaptonuria from birth, although the one was 70 years of age and the other 60 when the disease was first recognized The amount of homogentisic acid in the urine was determined by MacCallum in Seaborn s case, when the patient was placed on diets containing various amounts of protein As expected, a high protein diet resulted in increased excretion of this substance Table 1 gives the values obtained in this case

TABLE I

URINARY CONTENT OF NITROGEN AND HOMOGENTISIC ACID

	Total Nitrogen	*Homogentisic Acid*
Ordinary diet	1.04	0 161
High protein diet	1 17	0 240
Carbohydrate diet	0 87	0 170

Values in grams per 100 c c

The presence of alkaptonuria can be determined by dropping one drop of urine on a piece of sensitized photographic paper[38] The urine must first be rendered strongly alkaline by means of sodium hydroxide At the area of contact the paper turns black instantly Fishberg, who reported the test states that no other substance in urine will give this reaction

In theory the diet should contain a minimum of foods likely to result in the formation of tyrosine and phenylalanine from which homogentisic acid is derived such as barley wheat maize peas cows milk egg and shrimp In practice it is doubtful whether such restrictions would have any appreciable effect upon the course of the disease

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sulphuric acid solution, and (3) surgical solution of chlorinated soda Dilute ferric chloride added to the urine gives a black color, if melanin is present a transient blue color, if the pigment is homogentisic acid and none at all if it is carboluria

Lastly in a small number of cases no urinary pigment has been demonstrated, although the presence of the disease has been confirmed amply by the other features

Arthritis—The frequency of arthritis in ochronosis is high occurring in over half of all reported cases It commonly involves the spine and to a lesser extent, the shoulders, knees, and hips and usually is of the hypertrophic type Apart from eburnation of articular surfaces and the formation of osteophytes which are characteristic of osteoarthritis, there are changes in the skeleton which though not pathognomonic of ochronosis are extremely suggestive[3] These are (1) dense calcification of the intervertebral cartilages (2) granular osteoporosis or decalcification of the vertebrae (3) calcification of the spinal ligaments, (4) calcification of the costal cartilages Kalaczek[7] suggested the name of arthritis ochronotica for this type of arthritis, while Soderbergh[13] believes osteitis deformans ochronotica to be the better term In some cases the bony changes may be indistinguishable from those of osteomalacia except for the presence of the pigment and Puhr[8], who reported a case calls it osteomalacia all aptonurica

Prognosis and Treatment

Prognosis—The disease in the alkaptonuric or melanuric group runs a chronic course extending over years and terminates usually with some affection of the arterial system In the carbolic acid group the prognosis is good as the withdrawal of the solution will suffice to arrest the disease

Treatment—The treatment is largely one of prophylaxis such as the avoidance of the prolonged use of carbolic acid lotions, ointments or sprays The constant application of picric acid in treatment of extensive burns led in a case known to the author to early signs of the disease

Being either a congenital or familial disease, alkaptonuria can be prevented only by forbidding intermarriage in affected families When once the anomaly exists in an individual, all attempts to modify it are as yet unavailing

The ascorbic acid and other vitamins have been given to ochronotic patients in an attempt to influence the excretion of homogentisic acid but without effect [6, 31]

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CHAPTER IX A

THE PORPHYRINS AND THEIR RELATION TO DISEASE PORPHYRIA

By CECIL JAMES WATSON AND EVREL ARTHUR LARSON

TABLE OF CONTENTS

GENERAL NATURE OF THE PORPHYRINS

Definition — The porphyrins derive their name from the resemblance of their color to porphyry, ultimately from the Greek word, porphuros — crimson purple' The basic chemical structure[1] is the same for each porphyrin i e a porphin" skeleton composed of four pyrrol nuclei connected in a ring by methene bridges as shown in Fig 1

The individual porphyrins differ by virtue of varying substitution in the 8 positions noted in Fig 1 The term hematoporphyrin was introduced by Hoppe-Seyler to describe a substance obtained in vitro when hemoglobin was treated with sulphuric acid The substance was prepared first in pure form by Nencki and Sieber[3], who were responsible for the suggestion that hematoporphyrin was isomeric with bilirubin This incorrect belief was widely accepted and has persisted to some extent even in the light of exact knowledge of the structure of both substances The lack of finer spectroscopic methods as well as crystalline porphyrins for comparative purposes was responsible for the introduction of the term hematoporphyrinuria into the literature[4 5 6 7] Garrod[4] and others[5 6] were convinced that the porphyrin of the normal urine and feces and of the urine in various pathological states was identical with the hematoporphyrin of Nencki and Sieber While it is clear that Gunther [8] noted certain differences between hematoporphyrin Nencki and what he chose to call the "natural hematoporphyrin found in the urine in cases of congenital hematoporphyria', nevertheless Gunther is chiefly responsible for the wide usage of the latter term The chemical studies of H Fischer and his associates[1 9 10] have shown that the porphyrins occurring naturally are quite distinct from hematoporphyrin (see Fig 1), the latter substance has not been encountered in nature For this reason the term, porphyria, is preferable to hematoporphyria The term porphyria should be reserved to designate a relatively rare group of diseases in which excessive porphyrin formation is clearly a metabolic fault in other words to use Garrod s expression an inborn error of metabolism' This error consists of the formation and excretion of uro- or uro-type porphyrins It may be emphasized that these are abnormal insofar as human excreta are concerned Rimington in a personal communication states that minute traces of a uroporphyrin occur in normal urine We have been unable thus far, at least to detect it, but this may relate to the quantities studied

Physicians commonly associate the term porphyrin only or mainly with the rare disease porphyria, while as a matter of fact the physio-

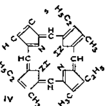
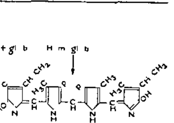
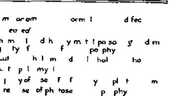
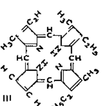
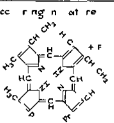
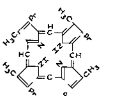
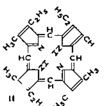
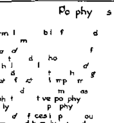
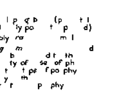
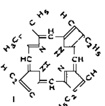
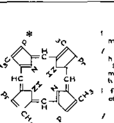
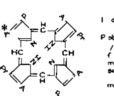













Fig 1 Chemical relationships of the porphyrins and data relating to their occurrence Formulae are from Fischer and Orth (11)

GENERAL NATURE OF THE PORPHYRINS

Definition. — The porphyrins derive their name from the resemblance of their color to porphyry, ultimately from the Greek word, porphuros — crimson", purple. The basic chemical structure[1, 2] is the same for each porphyrin, i.e. a "porphin" skeleton composed of four pyrrol nuclei connected in a ring by methene bridges as shown in Fig. 1.

The individual porphyrins differ by virtue of varying substitution in the 8 positions noted in Fig. 1. The term hematoporphyrin was introduced by Hoppe-Seyler to describe a substance obtained in vitro when hemoglobin was treated with sulphuric acid. The substance was prepared first in pure form by Nencki and Sieber[3], who were responsible for the suggestion that hematoporphyrin was isomeric with bilirubin. This incorrect belief was widely accepted and has persisted to some extent even in the light of exact knowledge of the structure of both substances. The lack of finer spectroscopic methods as well as crystalline porphyrins for comparative purposes was responsible for the introduction of the term hematoporphyrinuria into the literature[4, 5, 6, 7]. Garrod[4] and others[6] were convinced that the porphyrin of the normal urine and feces and of the urine in various pathological states was identical with the hematoporphyrin of Nencki and Sieber. While it is clear that Gunther[7, 8] noted certain differences between hematoporphyrin Nencki and what he chose to call the "natural hematoporphyrin" found in the urine in cases of congenital 'hematoporphyria', nevertheless Gunther is chiefly responsible for the wide usage of the latter term. The chemical studies of H. Fischer and his associates[1, 9, 10] have shown that the porphyrins occurring naturally are quite distinct from hematoporphyrin (see Fig. 1), the latter substance has not been encountered in nature. For this reason the term, porphyria is preferable to hematoporphyria. The term porphyria should be reserved to designate a relatively rare group of diseases in which excessive porphyrin formation is clearly a metabolic fault in other words, to use Garrod's expression an 'inborn error of metabolism'. This error consists of the formation and excretion of uro- or uro-type porphyrins. It may be emphasized that these are abnormal insofar as human excreta are concerned. Rimington in a personal communication states that minute traces of a uroporphyrin occur in normal urine. We have been unable thus far, at least, to detect it but this may relate to the quantities studied.

Physicians commonly associate the term porphyrin only or mainly with the rare disease porphyria, while as a matter of fact the physio-

porphyrin IV[10] It was found that the mesoporphyrin obtained from hemoglobin was mesoporphyrin 9 in Fischer's classification Since an equal number of protoporphyrin isomers are theoretically possible the correct designation of the protoporphyrin from hemoglobin is likewise 9 , although in Fig 1 it has been designed III simply to indicate to which aetioporphyrin it corresponds In the case of copro- and uro-porphyrin the numbers I and III are applied directly since there are but four possible isomers of each of these As indicated in Fig 1 bilirubin likewise has been shown to correspond in configuration to aetioporphyrin III[12] There is considerable evidence that its formation is by virtue of an oxidative removal of the CH bridge between pyrrol nuclei I and II although the mode by which this is effected in nature is unknown

The formation of large amounts of copro- and uro porphyrin I such as characterized the famous case Petry from whose urine and feces these porphyrins were first isolated was regarded by H Fischer as an expression of atavism a return on the part of the human organism to a long forgotten mechanism such as that normally employed by the African bird Turacus in whose wing feathers the red pigment turacin is composed of the copper salt of uroporphyrin According to Fischer[154] this is the type I isomer but more recently Rimington[13] reports isolation of type III uroporphyrin from turacin This question requires further study The suggestion of atavism in the case Petry was strengthened considerably when the chemical study of material obtained at necropsy revealed that the bones contained large amounts of uroporphyrin I and that this was present in the scapula[155] in the form of the copper salt in other words as turacin While such an extreme and bizarre overproduction of porphyrin may well represent a rare form of atavism it has become increasingly evident as a result of recent studies which will be mentioned subsequently that very small amounts of coproporphyrin corresponding to aetioporphyrin I are manufactured by the normal individual although for what purpose is not yet clear It appears that the dualism of the porphyrins is physiological under normal circumstances the amounts of porphyrin of type I which are formed are infinitesimal in comparison with those of type III It is generally held that transition from type III to type I or vice versa does not occur since this would involve rotation of pyrrol nucleus IV through an angle of 180 (see Fig 1) which in effect would require destruction and resynthesis of the porphyrin molecule Porphyrins corresponding to aetioporphyrin II or IV have not been encountered in nature

logical porphyrins such as proto- and copro-porphyrin are of much greater everyday significance, variation of amounts of these porphyrins in disease, as discussed in the following pages, should not be referred to under the heading of porphyria

Hans Fischer's terminology of the porphyrins has been accepted most generally The first porphyrin which he named was isolated from the urine of a case of porphyria and was believed not to occur in the feces, hence it was named uroporphyrin Subsequently another new porphyrin was isolated from the feces of the same case, this was named coproporphyrin Later it was determined that small amounts of copro porphyrin are also present in the urine even normally, and more recently uro-type porphyrins have been isolated repeatedly from the feces of cases of porphyria, thus the terms have relatively little significance in the original sense in which Fischer used them, nevertheless the amount of coproporphyrin in the feces usually is much larger than in the urine and the opposite is true for the uro type porphyrins in cases of porphyria

The term coproporphyrinuria literally means "feces porphyrin in the urine" The available evidence, however, favors the view that the urinary coproporphyrin does not originate in the intestinal tract but rather that it is at least in the main, an endogenous metabolite

The porphyrin problem is considerably more complex because of the occurrence of isomers The four aetioporphyrins constitute the basis for Fischer's classification of the porphyrin isomers[1,2,11] The aetiopor phyrins are relatively simple having only ethyl and methyl side groups in equal number All four were synthesized and were shown to have the structure noted in Fig 1 The copro- and uro porphyrin first isolated by H Fischer from a case of congenital porphyria were found to have an arrangement of side chains corresponding to that of aetio porphyrin I, hence these were classified as copro- and uro porphyrin I Subsequently it was determined that the protoporphyrin in the hemo globin molecule in this case as well as in the normal corresponded in structure to aetioporphyrin III (see Fig 1) This finding was the basis for H Fischer's "dualism" of the porphyrins, which, as will be apparent in the following is of considerable significance in a variety of diseases

In identifying the porphyrin isomers the ester melting points were found to be of decisive value The aetioporphyrins, however are not of practical value because of their inability to form esters Fischer consequently made use of the easily prepared mesoporphyrins, of which there are fifteen possible isomers two corresponding to aetioporphyrin I three to aetioporphyrin II, six to aetioporphyrin III and four to aetio

Chemical and Physical Properties of the Porphyrins

Color and Absorption Spectra — The red color of the porphyrins varies considerably in character under different conditions All aline solutions are reddish brown while solutions in mineral acids are reddish violet or purple In organic solvents even in the presence of organic acids as for instance in ether and acetic acid the color usually is a dull red Of the porphyrins occurring naturally protoporphyrin has the most distinctive color quite in accord with its considerably different absorption spectrum (see Table I) solutions of protoporphyrin have a somewhat more bluish shade even in organic solvents In the solid state the color of the porphyrins is quite similar to that of their solutions although it usually tends to be darker or less brilliant The crystalline esters of the various porphyrins have much the same color as their chloroform solutions i e a pure deep red

The absorption spectra of the porphyrins are fairly distinctive Identification by this means however requires a spectrometer precise within five Ångstrom units The apparatus should have cross hairs permitting exact definition of the absorption maxima It is helpful also if it permits superimposition of the spectrum of a known pure porphyrin in the same solvent The Lowe Schumm (Zeiss) spectrometer or the Hartridge reversion spectroscope is quite satisfactory The position of the absorption bands of a few of the more important porphyrins is noted in Table I

The closely similar absorption of copro and hemato-porphyrin as already noted was responsible for the earlier failure to distinguish them The relatively slight differences in position of absorption bands as seen when the spectra of the two porphyrins are superimposed is again evident in Fig 2

Although porphyrins with different groups on the porphin ring are readily distinguished spectroscopically the isomers as for instance the four isomeric coproporphyrins are spectroscopically identical Complex metallic compounds of the porphyrins exhibiting two banded spectra are encountered commonly in nature[6, 8, 15, 16, 16]

Red Fluorescence and Fluorescence Spectra — The porphyrins are characterized further by exhibiting intense red fluorescence when excited by the longer wave lengths of ultraviolet light[16, 18, 19, 20] such as the suitably filtered light from a mercury quartz lamp Maximum fluorescence is produced by light in the region of 4000 Å The red fluorescence is not entirely specific for the porphyrins which are of clinical interest

TABLE I*

Solvent	*Ether*					*7.5 N HCl*				
Band (max abs.)	I	II mμ	III	IV	Order of Intensity	I	II mμ	III	Order of Intensity	*HCl No*
Protoporphyrin	632.5	585.1	536.8	601.9	IV I III II	602.4	582.2	557.2	III I II	0.6N
Deuteroporphyrin	621.7	566.8	5 5.9	494.1	IV III I II	592.4	572.6	549.3	III I II	0.1N
Coproporphyrin	6 3.9	568	5 9.3	497.9	IV I III II	593.9	574.6	550.9	III I II	0.03N
Uroporphyrin I in n/10 NaOH	Insoluble in ether					597.0	55 .8	410.3	III II I	none
Waldenstroms Porphyrin	Insoluble in ether					59 .8	552.6	408.7	III II I	none
Hematoporphyrin	6 4.8	569.0	530.4	496.5	IV III II I	59 .8	57 .5	551.7	III I II	0.036N

Composed in part from data given by Kirstahler[14]

by chloroform and yield readily soluble sodium compounds The hydrochloric acid fractionation of the porphyrins, based upon varying relative solubility in ether and in hydrochloric acid has proved of great value in separating them [14] The HCl number ordinarily has been defined as the per cent content* of HCl which removes two thirds of the porphyrin from solution in ethyl ether when equal volumes are thoroughly shaken together Thus the chlorophyll porphyrins are characterized by HCl numbers above 5, while those of more immediate clinical interest such as proto-, deutero- and copro-porphyrin are . or less (see Table I) The isomers of any of the porphyrins have the same HCl number Uroporphyrin I and the Waldenstrom porphyrin being insoluble in ether, do not have HCl numbers The latter porphyrin however may be partially extracted from the urine by ethyl acetate at pH 4 0

Differential Characteristics of the Isomers — The crystalline methyl and ethyl esters of the porphyrins as well as many of their metal complexes have sharp melting points which are distinctive The methyl esters are studied most often (see Table II) The manner of crystallization and the crystal form of these compounds are of some value, usually however not decisive

The pH fluorescence curves ' of the various porphyrin isomers have been shown to differ in a constant way[~ 6 7] These curves depend upon specific variability in intensity of fluorescence in the iso electric

TABLE II

Melting Poi ts of the Esters of the Naturally Occurring Porphyrins

Ester	M.P C
Coproporphyrin I tetramethyl ester	248 252
Coproporphyrin I tetraethyl ester	225 226
Coproporphyrin III tetramethyl ester	135 144 167 170 (dimorphic)
Coproporphyrin III tetraethyl ester	1 6 (not sharp)
Protoporphyrin IX dimethyl ester	2 8
Deuteroporphyrin IX dimethyl ester	218 2 0
Deuteroporphyrin IX diethyl ester	04
Uroporphyrin I octamethyl ester	284
Waldenstroms porphyrin methyl ester	250 270 usually 258 260

Commercial concentrated HCl is 37 38 per cent 10 per cent strength is prepared by diluting 10 c.c of the concentrated to 37 c.c with distilled water or 1 per cent by diluting 1 c.c to 37 c.c although it is traditional to express the HCl No in per cent. undoubtedly this has given rise to confusion and therefore for some time we have expressed it in terms of normality (see Table I)

chief among the substances, which may cause confusion, is chlorophyll or one of its porphyrin derivatives Fortunately these are separated rather easily from the former group on the basis of differing solubilities [1 3 4] The red fluorescence is associated with a strong fluorescence spectrum which is characteristic for the species of porphyrin but has not been found to distinguish isomers The fluorescence spectrum (see Fig 2) has been used to identify intracellular porphyrins as studied with a spectral analytical microscope [9] With this apparatus cells con

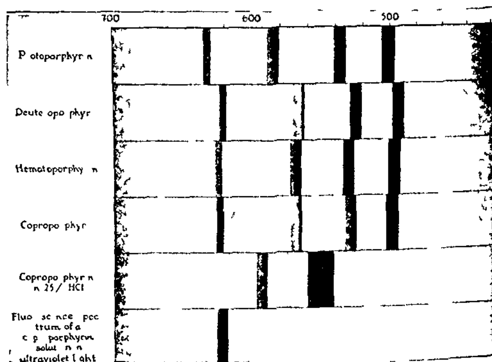


Fig 2 Absorption spectra of some of the more important porphyrins The porphyrins were dissolved in ether and acetic acid except where otherwise noted

taining porphyrin are first identified by virtue of their red fluorescence, then the fluorescence spectrum is measured

Solubilities – The porphyrins occurring naturally may be divided into two main groups on the basis of their behavior toward chloroform and sodium hydroxide [14] The porphyrins most nearly related to hemoglobin i e proto and deutero porphyrin are chloroform soluble and yield insoluble sodium salts This is true also of artificial hematoporphyrin Copro and uro porphyrin are not extracted from dilute HCl

The following method[195] may be recommended for both qualitative and quantitative purposes 5 c c of the mixed 24 hour urine sample are added to 20 c c of 1 per cent aqueous sodium acetate solution in a separatory funnel Then 5 c c of buffered glacial acetic acid (4 parts glacial acetic acid to 1 part of saturated sodium acetate solution) are added after which thorough shaking is carried out with 100 c c of ethyl acetate This mixture then is washed once with 20 c c of 005 per cent iodine in 1 per cent sodium acetate solution and twice with 20 c c portions of 1 per cent sodium acetate solution without iodine The iodine solution serves to convert any colorless precursor or chromogen[196] of coproporphyrin to porphyrin so that it will be included in the determination If uro-type porphyrin is present, red fluorescence will be apparent *often in the sodium acetate washes coproporphyrin how*-ever, is not extracted even in traces The ethyl acetate then is extracted by 5 c c portions of 1 5N HCl Each of these should be viewed for red fluorescence until it is certain that the extraction is quantitative The combined HCl is measured and the amount of porphyrin is determined by fluorimetry For normal urine or urine containing small amounts of porphyrin a sensitive fluorophotometer[195] is required Nevertheless the use of a light source as described below permits one to employ this method in roughly quantitative fashion either by comparison with *similar solutions obtained from normal 24 hour samples or preferably*, with a series of reference solutions containing known amounts of coproporphyrin in 1 5 normal HCl While by no means precise this does enable one to determine significant deviations from normal It is essential however that a suitably filtered light source be used[19] This consists of a strong source of near ultra violet light the filter characteristics being such that the principal light is that in the region of 4000 A with little or none at 3650 A the latter exciting blue and green fluorescence of other compounds which masks the red fluorescence of the porphyrins

Previous methods of porphyrin analysis[33 34 5 36 37] have failed to recognize that significant fractions are excreted as chromogen though there can be little doubt that this was known to Saillet[6] half a century *ago This has been studied recently in detail*[196]*, and as a result of this* study the iodine wash is included in the above technique

The Ehrlich aldehyde reaction is carried out in the usual way[30] on a small portion of a 24 hour urine sample If positive the chloroform solubility of the aldehyde compound should be determined as that of porphobilinogen is insoluble in chloroform, while the urobilinogen

zones of the porphyrins All of these methods, however, require a relatively considerable amount of pure porphyrin, and thus are not applicable to the problem of isomer analysis in small amounts of material as for example the coproporphyrins (I and III) of normal urine It has been shown in recent years that the ratio of the latter may be determined on the basis of differential precipitation or "fluorescence quenching" in 35 per cent aqueous solution of acetone[29] This method is applicable to but a few micrograms of coproporphyrin, so that the isomer ratio may be determined with as little as 100 c c of urine or even less when the initial concentration is high

Methods of Detection and Estimation

Urine and Feces – Appreciable quantities of porphyrin impart to the urine a reddish brown or wine red color In this event the HCl absorption spectrum (see Fig 2) is readily observed and is seen to be intense after acidifying a few cubic centimeters of the urine with concentrated hydrochloric acid This simple method at once serves to distinguish porphyrinuria from hemoglobinuria Amounts sufficient to discolor the urine are encountered most often in porphyria In the symptomatic or secondary porphyrinurias, as for example in lead poisoning, the amount rarely is sufficient to produce gross discoloration of the urine, although occasional cases of this type have been reported[195] It may be emphasized that in porphyria the color of the freshly voided urine may be relatively normal due to the presence of colorless precursors or chromogens (see a later paragraph)

Since the urine always contains at least a small amount of coproporphyrin qualitative tests are of relatively little value except to distinguish the species of porphyrin or to be employed in a roughly quantitative manner The latter applies only in the case of outspoken variations and even then depends upon individual orientation and a uniform technique which ought to take into account the dilution of the urine The detection of porphyrin in the urine by means of red fluorescence in ultraviolet light is a great deal more sensitive than spectroscopy, assuming a certain degree of preliminary purification On the other hand, many compounds in the native urine tend to mask the red fluorescence with the result that spectroscopy is often more sensitive after acidification with hydrochloric acid

of saturated aqueous sodium acetate solution after which the porphyrins are again taken into ether. Extraction with 5 per cent HCl serves to remove the porphyrins of principal physiological importance, the chlorophyll derivatives remaining in ether. A double spectrum is encountered commonly in the 5 per cent HCl due to the presence of both proto- (max absorption at 556 mμ) and copro porphyrin (max absorption at 548 mμ).

Protoporphyrin in the feces is partly endogenous, partly exogenous, the latter being derived from dietary hemoglobin[38, 40, 41, 4]. The amount is increased by the addition of meat to the diet or the presence of blood in the intestinal tract. The endogenous fraction probably represented by the small amounts of protoporphyrin demonstrable in the bile[38] may be derived from the bone *marrow*[53] or erythrocyte protoporphyrin. So far as is known, deuteroporphyrin 9 (isomer type III)[43] is formed solely by putrefaction of hemoglobin in the bowel and its detection, therefore, is of specific value in the search for occult bleeding, assuming that extrinsic sources of hemoglobin have been excluded. In Fig. 2 it will be noted that the absorption spectra of copro- and deutero porphyrin are very similar. The latter porphyrin is chloroform soluble and may be separated from coproporphyrin by extraction with chloroform from 0.2 per cent hydrochloric acid[2, 22, 39, 45]. This does not serve to separate deutero from the "pseudodeutero porphyrins," whose significance has not been determined[9]. Thus the detection of deuteroporphyrin, although probably of specific value, is necessarily a much more complex procedure than was the original porphyrin test for occult bleeding[44].

Relatively little *information* is available as to the fractional quantitative determination of the fecal porphyrins[3, 39, 47]. The above method for the urine has been applied satisfactorily to feces by including a chloroform extraction from a 0.1N HCl solution, to separate copro porphyrins from the chloroform soluble proto and deutero-type porphyrins. Coproporphyrin I and III occur simultaneously in the feces and recent study indicates that the "fluorescence quenching" technique as previously referred to, is applicable, although but little data have yet been accumulated.

Erythrocytes and Serum.—van den Bergh and his associates[19, 48, 49] gave particular attention to the detection and estimation of the protoporphyrin in the erythrocytes and blood serum. They employed a fluorocolorimetric procedure which provided but a rough estimation. The amount of protoporphyrin in the red blood cells *is so small that a*

aldehyde is readily extracted[31] It should be noted, however that in the presence of large amounts of urobilinogen it may not be possible to extract all of the aldehyde compound This but rarely offers difficulty as porphyria urines seldom contain more than traces of urobilinogen

Uro type porphyrins (such as the Waldenstrom porphyrin) if any are present may be detected in the sodium acetate wash' To be certain larger amounts may be concentrated by mixing several hundred *ml of urine with 20-25 gm* talc *after acidification with the buffered* acetic acid This then is collected on a small Buchner funnel and dried by tamping With the suction off, the talc then is covered with 10 c c of 1 per cent NaOH, after a few moments the suction is turned on and the NaOH solution is collected in the flask below This solution should be studied spectroscopically The porphyrin may be present as the zinc complex with a two banded spectrum about 580 and 540 mμ or in the free state in which event at least four bands will be visible the most distinctive being that with a maximum at 612 mμ It should be noted however, that the metal complex is much more readily adsorbed than the free porphyrin If concentrated HCl is added to the NaOH in sufficient amount to make a 1 per cent solution the HCl spectrum will now be seen (see Table I) An approximate quantitative determination with a fluorophotometer may be carried out but the presence of uroporphyrin I or the Waldenstrom porphyrin is of itself sufficient for the diagnosis of porphyria If the first 10 c c of 1 per cent NaOH from the talc as described in the foregoing do not have demonstrable porphyrin one may safely assume that uro-type porphyrins are not present If however considerable porphyrin is found in the first 10 c c additional extractions of the talc should be carried out assuming that a quantitative determination is planned It should be noted that the latter is of some value in following the course of the disease, since marked diminution in amount is characteristic of remissions in most instances

H Fischer[33] *first applied the acetic and ether extraction* method to the feces Ten grams of feces were ground in a mortar with 10 c c of glacial acetic acid After addition of considerable ether and further grinding the mixture was filtered More ether was added to the filtrate and this was washed with water repeatedly The porphyrin then was extracted with 25 per cent HCl and the solution was examined spectroscopically Because of the presence of porphyrins derived from chlorophyll as well as other impurities further purification is desirable The hydrochloric acid solution may be made Congo negative by the addition

phyrin Iodine is efficient in this regard for coproporphyrin but heat is much more efficient in the case of uro type porphyrins Here as much as ninety per cent of the total porphyrin may be excreted as a chromogen and thus overlooked unless heat is first employed[164,167]

Biological Activity of the Porphyrins

The light sensitizing (photodynamic) activity of the porphyrins was the first biological effect to be recognized[4] and has received the most study[5,58,7,8,59] Light exposure in the presence of hematoporphyrin has been shown to cause hemolysis of erythrocytes and death of paramecia Exposure to strong light subsequent to injection of a *suitable porphyrin solution causes death or severe injury in animals or* man The occurrence of light stroke or acute Lichttod in animals is dependent upon the amount of porphyrin administered and the subsequent degree of exposure to light[4,5] In the most rapidly fatal type the animal becomes restless the skin is seen to become increasingly livid the blood pressure falls coma and death ensue With less porphyrin or less light there may be an initial rise in blood pressure followed before death by a marked fall, paroxysmal dyspnea and a marked generalized erythema are prominent These latter animals may recover if protected from further light exposure during the early stage of the symptoms With still less porphyrin or less light exposure the animal may survive but develops dermatitis in the area of exposure This is characterized by edema and erythema White mice which are particularly suitable for these experiments exhibit the most marked changes in the ears nose and tail where areas of necrosis may appear particularly when por*phyrin administration and light exposure are maintained for some time* in repeated small doses (chronic light sickness) In this event loss of hair likewise is observed *In the only human experiments which have* been recorded[9,60] entirely similar changes except for necrosis were observed on the parts of the body exposed to light These manifestations followed the intravenous injection of 0 2 gm of hematoporphyrin Nencki in the well known self experiment carried out by Meyer Betz[59] (see Fig 3)

It is well recognized that light sensitizing effect and red fluorescence in ultraviolet light are correlated phenomena Thus the free porphyrins are capable of producing both but porphyrinogens and the complex

very sensitive method either fluorimetric or spectrophotometric is desirable For details of the methods the original papers should be consulted[0 103 171]

Schwartz and co-workers[1 7] recently have demonstrated that the circulating erythrocytes contain copro- as well as proto porphyrin They have described a fractional method which is applicable also to bone marrow and by means of which Schmid and co-workers[1,8] have shown that striking differences often exist in the concentrations of bone marrow versus circulating erythrocyte porphyrins (see section on physiological functions) Uroporphyrin I recently has been isolated in crystalline form from the circulating erythrocytes of a human case of porphyria[1 9] having previously been obtained from the erythrocytes of cattle having porphyria[160] and from the bone marrow of Petry, the famous case of porphyria studied by Fischer and co-workers[1,5] and by Borst and Konigsdorffer[0]

Although copro- and uro-porphyrin have been noted in human blood serum in sufficient amount for purposes of spectroscopic identification[38 189] the amounts more often are so small that red fluorescence again must be depended upon Extraction of coproporphyrin from the serum by means of glacial acetic acid and ether or ethyl acetate has been employed preliminary to fluorocolorimetry or fluorimetry[38 48 189]

Isolation of Porphyrins Occurring Naturally

In the main two methods have been employed for the isolation of crystalline porphyrins The first is the acetic and ether or ethyl acetate extraction which is quite satisfactory for coproporphyrin in urine and feces[3 38 45] The second is the chromatographic procedure as applied by Waldenstrom and further elaborated by others[17 51 2] This is of particular use in isolating the ether insoluble porphyrins but can be employed also in separating and purifying other porphyrins Rimington[161] and Prunty[16] recently have used paper chromatography to advantage in identifying and isolating small quantities of the porphyrins in natural materials Sveinsson and Rimington[163] have described a useful method of separation and isolation of uro- and copro porphyrins from urine depending on adsorption by $CaHPO_4$

Recent studies[3 164 16 16 19 116] have emphasized that larger yields may be obtained if any fraction excreted as chromogen is converted to por

that uroporphyrin is more light sensitizing in animals than is coproporphyrin, a difference which again was thought to depend upon the number of carboxyl groups[4] On the other hand hematoporphyrin with but two carboxyl groups is much more light sensitizing than coproporphyrin which has four Protoporphyrin which also has two is least photosensitizing[4] Thus it is unlikely that the number of carboxyl groups is decisive, rather it is probable that molecular arrangement and resonance are the critical factors

As will be seen later the cutaneous forms of porphyria i e those in which light sensitivity is most prominent usually excrete large amounts of uroporphyrin I together with some coproporphyrin while the 'abdominal and "nervous types are characterized by excretion of smaller amounts of porphyrin either uro-type (Waldenstrom) coproporphyrin or a mixture

In the latter forms most of the porphyrin is excreted as the metal (zinc) complex while in the pure photosensitive or so called congenital porphyria the porphyrin is free The possibility has been considered that the combination with metal prevented photosensitization It is true that the zinc complex does not exhibit as intense a fluorescence as the free porphyrin nevertheless cases of the mixed type of porphyria have been observed now in which photosensitivity was present yet the urine collected in pyrex flasks to avoid external contact with zinc exhibited only the zinc complex spectrum of the porphyrin

In addition to their photodynamic activity the porphyrins are capable of producing smooth muscle spasm The application of very dilute solutions of various porphyrins to an exposed loop of bowel results in a prolonged spasm intractable to atropine but relaxed by adrenalin[61] This has been confirmed by Chadbourn in unpublished work done by this laboratory

Intestinal colic as well as vasospastic sequelae such as hypertension oliguria spasm of retinal vessels and even peripheral neuritis are regarded by some authorities[43 6] as porphyrinopathic phenomena regardless of whether they are observed in idiopathic porphyria or in toxic states such as lead poisoning On the other hand recent studies[16] have indicated strongly that abdominal and nervous manifestations and hypertension are much better correlated with the amount of urinary porphobilinogen than with porphyrin itself There is also indication that abnormal amounts of certain porphyrins or their precursors or derivatives condition endocrine abnormalities Hyperthyroidism men

metallic salts such as those of iron and copper, are neither fluorescent nor light sensitizing. These two correlated phenomena are not specific characteristics of the porphyrins. A number of fluorescent dyes of which eosin and rose Bengal are examples, are light sensitizing substances. Pimenta de Mello[166], in this laboratory, recently has discovered that one of the photodynamic effects of rose Bengal in rabbits is to cause a marked increase of urinary coproporphyrin (type III).



Fig 3. Self experiment by Meyer Betz showing the effect of exposure to light following hematoporphyrin injection.[9] (From Meyer Betz, Deutsch Arch f klin Med 1913 CXII 112)

Gaffron[8] found that porphyrins in the presence of light are capable of acting as catalyzers in the transfer of oxygen to protein. Of the various porphyrins studied, uroporphyrin possessed this photodynamic activity to the most marked extent and because of this it was believed that the activity was in some way dependent upon the number of carboxyl groups in the molecule[6] (see Fig 1). It had been shown earlier

that uroporphyrin is more light sensitizing in animals than is coproporphyrin a difference which again was thought to depend upon the number of carboxyl groups[8] On the other hand hematoporphyrin with but two carboxyl groups is much more light sensitizing than coproporphyrin which has four Protoporphyrin which also has two is least photosensitizing[6] Thus it is unlikely that the number of carboxyl groups is decisive rather it is probable that molecular arrangement and 'resonance' are the critical factors

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strual irregularities, hirsutism, sexual precocity and gynecomastia have all been observed in association with porphyrin Porphyrin administered to mice is said to cause a more rapid maturation of ova[63] and in spayed mice a resumption of oestrus[64]

THE OCCURRENCE AND POSSIBLE FUNCTIONS OR SIGNIFICANCE OF THE PHYSIOLOGICAL PORPHYRINS IN MAN (OTHER THAN THE METALLO PORPHYRIN-PROTEIN COMPLEXES)

Normally the amount of porphyrin in the body, exclusive of that contained in hemoglobin, myohemoglobin and cytochrome, is extremely small Van den Bergh and Hyman[19] first reported the presence of free protoporphyrin in the erythrocytes and Grotepass subsequently isolated protoporphyrin 9, corresponding to aetioporphyrin III[65] Subsequent studies have confirmed this observation[66] and have indicated that several factors appear to determine the amount of the EP (erythrocyte protoporphyrin), i e (1) increased reticulocyte percentage or normoblastic hyperplasia in the bone marrow, (2) iron deficiency or factors interfering with utilization of iron in hemoglobin synthesis, (3) the formation of protoporphyrin from hemoglobin in sequestered erythrocytes. This is the least well documented and probably the least important of the three Its inclusion rests on the observation[66] that the EP increases when erythrocytes are incubated in vitro under sterile precautions and also during splenic stasis

Reticulocytes are relatively rich in protoporphyrin[67], but the protoporphyrin concentration of the red cell is not always correlated with the reticulocylte percentage [66] Thus in iron deficiency anemia the reticulocyte percentage may be normal or but slightly increased, while the EP is markedly elevated The normal range of erythrocyte protoporphyrin (EP) concentration is believed to be from 15 to 60 micrograms per 100 c c of cells[168, 169], although higher values for supposedly normal persons have been reported by others[170, 171] The available evidence indicates that the main formation of the EP is closely associated with hemoglobin synthesis in the maturing normoblasts but to a much lesser extent in megaloblasts[66] Cartwright and Wintrobe[69] recently have shown that pyridoxine deficiency in swine is characterized by hyperferremia with normal or low values for EP These animals exhibit hypochromic

anemia and evidently are not utilizing iron This is in contrast to the hypochromic anemia of simple iron deficiency in which the EP is markedly elevated Thus it is suggested that in swine pyridoxine is essential to protoporphyrin and hence to hemoglobin synthesis Whether this is true for man remains to be determined thus far at least human hypochromic anemias with normal or reduced EP have not been described

The erythrocyte protoporphyrin (EP) is increased to the most marked degree under two conditions 1) iron deficiency 2) heavy metal poisoning It is increased also moderately in the hemolytic anemias and to a lesser extent although as a rule significantly in the refractory (hyporegenerative or aplastic) anemias It is normal or low in pernicious anemia possibly also in erythroblastic anemia although in the latter instance further studies are needed

The recent recognition[157, 159] of the presence of very small amounts of copro- in addition to proto porphyrin in erythrocytes has led to an intensive study of the ECP (erythrocyte coproporphyrin) in the human being under normal and pathological circumstances[164] The normal concentration is from 0 to 2 Mg per 100 c c of erythrocytes The greatest increases are observed in the hemolytic anemias while in pernicious anemia in relapse none has been demonstrable After vitamin B_{12} therapy a striking increase is noted which is closely correlated with the reticulocyte percentage the peak ECP lags very slightly behind the reticulocyte peak while, as previously shown[66] the peak EP concentration under these circumstances is considerably later In general the correlation of the ECP with the reticulocyte percentage is highly significant though occasional deviations have been noted as in certain cases of lead poisoning It appears that the ECP is a sensitive chemical index of the rate of hemoglobin synthesis, or attempted synthesis in the bone marrow In support of this view it has been found more recently[1, 3] that the bone marrow contains larger amounts of coproporphyrin than the circulating erythrocytes in states of heightened erythropoietic activity marked increases are observed and in several situations such as lead poisoning or post hemorrhagic anemia the copro-proto ratio is high in the bone marrow and simultaneously low in the circulating red cells This harmonizes well with a concept recently expressed[11, 13] that coproporphyrin III is a normal intermediary in hemoglobin metabolism a direct precursor of the hemoglobin protoporphyrin Other possibilities however are not excluded[1, 2]

The normal daily excretion of urinary coproporphyrin as determined with a modification[8] of the Fikentscher ether extraction method, indicated that the normal range of 24 hour values was from 20 to 100 Mg[37,1,4] Recent studies have shown, however, that this figure must be revised upward by a factor of three This is due in part to chromogen, hitherto not included, to better preservation by alkalinization of the urine during collection and to improved fluorimetry The new method[32], as described in the foregoing embraces these refinements and consequently yields a mean normal value of 157 Mg per day with a range of 68 to -79 Mg (82 individuals) The isomer distribution, as previously reported[1,4] is unaffected by this revision of the total UCP value This is from 48 to 9- per cent type I and from 8 to 5- per cent type III At least 90 per cent of normal individuals excrete from 60 to 90 per cent of type I isomer The range of excretion of coproporphyrin in the normal feces is probably from 1,0 to 400 micrograms per day, although insufficient data are available to establish accurate limits

Recent papers[16,10,169,183,184] consider in some detail the several theories relating to the origin of the coproporphyrin of the normal feces, bile and urine Yeast cells and bacteria synthesize coproporphyrin with ease[1,8,86,17], it is evident that protoporphyrin is formed readily in the animal body by the utilization of simple precursors i e acetic acid and glycine Recent studies[2,176,1,1,8,1,9,180,181] reveal that the same building blocks are used in the biosynthesis of copro- and uro-porphyrin

The total production of coproporphyrin I in animals and man appears to be related to the total erythropoietic activity or more exactly the rate of hemoglobin formation in the bone marrow Dobriner and Rhoads[3] and Rimington[74] regard coproporphyrin I as a side product of hemoglobin synthesis the ratio of protoporphyrin to coproporphyrin, according to this theory, being about 10 000 to 1 Further studies are needed with reference to total coproporphyrin I production in various abnormal states in man, associated with increased or decreased production of hemoglobin

Van den Bergh and his co workers[49] demonstrated an apparent transition of protoporphyrin to coproporphyrin by the liver in perfusion experiments but their results could not be confirmed by Watson and co-workers[7,188] Furthermore such a transition would not account for coproporphyrin I, the preponderant isomer of the bile, feces and urine under normal circumstances[37,9]

The exogenous theory has been given considerable credence in the

past[37, 47] chiefly because of the occurrence of minute amounts of proto or copro-porphyrin in many of the common foods[9, 10] and because of the apparent reabsorbability of porphyrins from the intestine[80] The idea has been held also that meat in the diet or gastrointestinal bleeding with consequent formation of porphyrin from hemoglobin was responsible for the normal urinary and fecal porphyrin content [1, 10] It was shown however that coproporphyrin and protoporphyrin[40] persist in the feces and urine of normal individuals on a vegetable diet furthermore the meconium contains relatively large amounts of coproporphyrin I[81, 82] The considerable increases of protoporphyrin 9 (III) and coproporphyrin I without hemoglobin in the feces of hemolytic jaundice patients[39] constitutes further evidence against these theories

A recent study[84] failed to confirm the reported increases in urinary coproporphyrin excretion following the feeding of hemoglobin[1,4], and isomer analysis did not show any augmentation of type III coproporphyrin excretion in such experiments Moreover the feeding of crystalline coproporphyrin I or III to humans produced neither an increase of UCP nor alterations in the isomer pattern Thus while the possibility of reabsorption of porphyrin from the bowel cannot be wholly excluded the contribution of this source to the urinary coproporphyrin probably is insignificant When complete biliary obstruction exists coproporphyrin is either absent from the feces or is present in amounts so small as compared with the normal that it may hardly be detected[39, 8] Regurgitation jaundice whether on the basis of mechanical obstruction such as stone or cancer or diffuse hepatic disease (cholangiolar functional impairment) is associated regularly with considerable increases of type I coproporphyrin in the urine[7, 18] This is most likely a diversion of porphyrin which would normally be excreted in the bile and feces The increased urinary excretion of coproporphyrin I in hepatitis and in many cases of cirrhosis is best ascribed to hepatocellular functional impairment The increased excretion of the type III isomer in the hepatic cirrhosis associated with chronic alcoholism[183, 184] and its concomitant nutritional deficiency is not well understood since these cases often exhibit just as much evidence of hepatocellular functional impairment as the cases of non alcoholic cirrhosis yet excrete type III rather than type I coproporphyrin The available evidence points to a close relationship in the production of the two isomers with a normal preponderance of type I but with overproduction of type III and relative or absolute depression of type I as a result of certain agents such as heavy

metals or chemicals including alcohol Of interest in this respect is the recent report of Kench and Wilkinson[86, 17] that yeast cells form coproporphyrin I in a glucose rich medium but coproporphyrin III under conditions of glucose poverty This at least indicates that alteration of environmental factors may affect the synthesis of the isomers in one direction or the other

The recent studies of alcoholism and cirrhosis on the one hand and of lead poisoning on the other strongly suggest that the disturbed porphyrin synthesis in the former is related to hepatic cellular metabolism that of the latter to hemoglobin synthesis in the bone marrow

H Kluver[87, 18] made the important discovery that the central nervous system of warm but not of cold blooded animals regularly contains small amounts of coproporphyrin tentatively identified as the type III isomer It occurs principally in the white matter unlike cytochrome which is more concentrated in the gray substance The amount of the nervous system coproporphyrin is very small, in the neighborhood of . to 4γ per 100 gm of brain[186] Its function is quite unknown Granick[89] and Gilder[89, 90] have suggested that it may be related to the control of oxygen utilization in view of the finding that it inhibits the activity of heme in the respiration of *H influenzae* This activity was believed due to competition by the coproporphyrin for a protein necessary to the formation of a heme catalyst[90]

Various attempts to alter the cerebral coproporphyrin or to affect brain function by means of additional coproporphyrin have met with negative results (unpublished studies with Frame Gellhorn, Chu and Wil off) The respiration of brain slices is unaffected by coproporphyrin III The injection of coproporphyrin III into the hypothalamus of living cats failed to produce any significant changes in behavior Injection of relatively large amounts of coproporphyrin III into the internal carotid artery of dogs 30 minutes before the animals were sacrificed did not result in any change in the cerebral concentration of porphyrin This would appear to indicate that the cerebral coproporphyrin is formed in situ not transported to the brain from another site of formation Acute and chronic pentobarbital intoxication in rabbits was unaccompanied by any change in the brain porphyrin concentration The same has already been reported for lead poisoning[186]

Uroporphyrin and Calcification — A number of reports indicate that uroporphyrin is related in some way to calcium metabolism, at least in so far as calcification of bone is concerned In the normal embryo and

to a lesser degree in post fetal life the bones exclusive of the bone marrow, contain considerably more porphyrin than in the adult[9] This is principally uroporphyrin which is present in largest amounts in the calcifying bone matrix during the 4th to 6th month of fetal life Uroporphyrin exhibits a distinct affinity for the bones when injected into young animals[31] Frankel[31] found that deposition did not occur if the animals were mature except during new bone formation as in a callus Deposition takes place to the most marked extent in the calcifying areas of the cartilage while no affinity is shown for cartilage which is not participating directly in the laying down of bone

It is worthy of note that certain other dyes notably rhodamin alizarin and carmin are deposited also in the metaphyseal area of the bone although not as intensely as is true of uroporphyrin[31] Rimington (personal communication) believes that the deposition of these substances as well as of uroporphyrin is related simply to adsorption by calcium phosphate as it is being deposited during new bone formation and that the uroporphyrin does not play any primary role in the calcification process

Increased Porphyrin Excretion Associated with Blood Diseases — Except for cases of idiopathic porphyria or coproporphyrinuria[9] in which the feces also contain marked excesses of coproporphyrin the largest amounts in the feces are found in patients with hemolytic jaundice[29] Distinct increases usually are encountered also in pernicious anemia[46 63] here the excretion is greatest during the period of reticulocyte response to liver therapy[29 63] The increases in these conditions are composed of coproporphyrin I and probably are related to increased erythropoietic activity The inconstant type I coproporphyrinuria of pernicious anemia and hemolytic jaundice is believed to be related to a variable disturbance of liver function Quite comparably a marked variation in excretion of urobilinogen in the urine has been observed in these conditions There is little reason to believe that hemoglobin catabolism per se results in the elaboration and excretion of coproporphyrin III as has been suggested[24]

The increased urinary coproporphyrin III excretion accompanying aplastic and hyporegenerative anemias[37 65] appears to be related to a disturbed hemoglobin synthesis on the basis of toxic or extrinsic chemical factors and indeed a history of chemical exposure often is evident[26] Hodgkin s disease especially in the terminal febrile stages commonly is accompanied by increases of UCP at times type I but in many

instances type III (work with S Hirsch to be published) In cases of leukemia inconstant mild increases of UCP have been found and in these the excess is type I Moderate absolute increases of the type III isomer are not uncommon in cases of cancer of the liver or biliary tract even though the preponderant isomer is type I[182] The significance of this finding is not yet clear When considered with the increased excretion of type III isomer in many cases of Hodgkin's disease, the question of endogenous chemical toxicity from necrotic tissue deserves investigation

The Urinary Coproporphyrin in Cases of Liver Disease and Jaundice — Garrod[4] was the first to emphasize the relationship of disturbed liver function to increased amounts of porphyrin in the urine He noted that gross or microscopic changes were often present in the liver in gout, acute rheumatism, leukemia, tuberculosis and other febrile conditions, in which the urine commonly exhibited an increased porphyrin content Increases were seen also in association with more obvious liver diseases such as cirrhosis or chronic passive congestion In recent years these findings have been confirmed[7, 84, 7, 98], and other diseases in which liver functional impairment is prominent, notably infectious hepatitis[97, 6, 97, 98, 99, 100], subacute atrophy and toxemia of pregnancy[101], have been found to be accompanied by an increased excretion of coproporphyrin in the urine Franke[10] found the excretion of urinary porphyrin uniformly increased in various types of liver disease, He noted also that alcohol has a distinct effect on the urinary porphyrin excretion in the normal individual, several glasses of beer or as little as 40 c c of cognac added to the diet were followed by significant increases Bacon and meat fat but not butter caused significant elevation It is noteworthy, however that no increase was observed following addition of .,000 gm of spinach to the daily diet This is important inasmuch as chlorophyll had been regarded previously as a possible source of urinary porphyrin

A recent study[184] has shown that most chronic alcoholics excrete excesses of type III coproporphyrin in the urine during periods of drinking, which commonly disappear following a variable period of abstinence and a normal diet

Studies of porphyrin excretion in jaundice have revealed significant elevation of the UCP in instances of mechanical jaundice[6, 97, 18] and in infectious hepatitis[97, 18.] In these the increase is due to the type I isomer, although as already mentioned cases of cancer of the biliary tract often exhibit moderate absolute increases of type III, even though type I is preponderant

Isomer analyses have revealed that a chemical difference usually exists between idiopathic non alcoholic cirrhosis as well as that following upon *infectious hepatitis on the one hand and that of the cirrhosis of chronic* alcoholism and malnutrition on the other the excessive UCP in the former being represented by the type I and in the latter by the type *III* isomer[27 183] In the case of alcoholic cirrhosis the increase of UCP often persists long after abstinence has begun in contrast to the alcoholic without cirrhosis in which it usually disappears relatively soon This difference may well be correlated with the factor or factors actually responsible for the cirrhosis

Increased Porphyrin Excretion Associated with Infectious Diseases — Since Garrod s studies a host of investigators have confirmed his observations on febrile porphyrinuria and their findings are summarized in *recent reviews*[37 47] *Carrie*[33] *added convincing* data on the close relationship between fever and increased coproporphyrin excretion in the urine Carrie felt certain that the increase *could be attributed to a* heightened rate of blood destruction and that the coproporphyrin therefore was type *III* It is clear however that another explanation must be sought since the porphyrin excreted is often at least the type I isomer[4 76] A more likely theory is that the excretion of coproporphyrin into the bile is hindered because of the adverse effect of fever or toxemia upon the liver Excluding certain virus diseases and instances in which administered drugs may have been contributory febrile states more often are attended by increased excretion of coproporphyrin I in the urine Although *further data are needed* with respect to the porphyrins in virus diseases it is clear that wide variations may be encountered *The two* virus *diseases* which have *been studied the most* in this regard namely infectious hepatitis[27] and acute poliomyelitis[101] are rather well differentiated on the basis of urinary coproporphyrin isomer analyses Thus uniform increases of the type I isomer are observed in the former especially during the icteric stage while the latter disease is accompanied rather regularly by significant and often marked increases of the type III isomer The reason for this difference has not been determined but the interesting question arises as to whether the neurotropic character of a virus is related to an increased excretion of type III coproporphyrin As already noted it probably is this isomer which is present regularly in the nervous system of warm blooded animals

Increased Porphyrin Excretion Associated with Metal and Chemical

Intoxication – The earlier observations of heightened urinary porphyrin excretion in lead poisoning[4] have been confirmed repeatedly[7, 47]. The marked increases are wholly accounted for by coproporphyrin III[6, 10, 106]. The amounts excreted are but rarely sufficient to produce red urine. Studies of the fecal porphyrin excretion in lead poisoning are very limited, the available evidence indicates that increases in both copro- and protoporphyrin occur[39], but in some instances at least the feces may contain only or principally coproporphyrin I at a time when the urine contains a marked excess of type III isomer.[6]

Salvarsan toxicity and chronic arsenic poisoning in humans[37, 107] as well as experimental arsenic poisoning in animals are associated with heightened excretion of coproporphyrin III in the urine. Mercury and bismuth, while capable of producing coproporphyrinuria type III in animals[108], have not been definitely proved to affect humans in similar fashion, although certain cases of chronic mercury intoxication in man have been observed in which excesses of the type III isomer in the urine were found[109].

Considerable confusion still exists with respect to the relation of sedatives to porphyrin excretion and porphyria. It has been observed repeatedly that sulfonal and trional administration may be followed by a syndrome closely resembling intermittent, acute idiopathic porphyria even to the excretion of uro-type porphyrins. Different investigators have isolated uroporphyrin I or a porphyrin of the Waldenstrom type[110]. The presence of a uroporphyrin in the urine from sulfonal poisoned rabbits has been reported[111], but Waldenstrom and Wendt[112] found only coproporphyrin III, and this has been our own experience in an unpublished study with H. Wiloff. Waldenstrom[113] reported that attacks of acute porphyria may be precipitated by the administration of trional to certain individuals previously symptomless but belonging to families in which other members had had spontaneous acute porphyria. It is thus possible that the activity of sulfonal and trional is merely one of precipitating an attack in an individual with a latent constitutional disease. Patients receiving paraldehyde, chloral hydrate, amylene hydrate and morphine may show moderate increases of urinary coproporphyrin[114]. Therapeutic doses of the barbiturates do not cause increased excretion, however instances of acute porphyria have been described following the prolonged use of phenobarbital[11], and uroporphyrin was tentatively identified in one case[116]. Again the possibility must be considered, as in the case of sulfonal and trional, that the barbiturate was merely the precipitating factor in a latent constitutional disease.

The sulfonamides and other aromatic amines have been reported to produce increases in urinary coproporphyrin III excretion in experimental animals[117] and significant increases have been observed often in human subjects following sulfonamide administration[118, 119] Increases of fecal coproporphyrin consisting preponderantly of the type III isomer also have been reported for sulfanilamide poisoned rats[118] Greenberg and Hoffbauer[16] recently have found that 80 to 90 per cent of the coproporphyrin normally excreted by rats is the type III isomer

Acute carbon tetrachloride[27] and methyl chloride intoxication in humans[1, 9] have been reported to cause marked type III coproporphyrinuria The same isomer was isolated from the feces in one of the latter instances

PORPHYRIA

It is perhaps impossible to draw a sharp dividing line between this group and the group of cases discussed in the foregoing As indicated at the outset the term porphyria connotes a marked overproduction of porphyrin as a constitutional fault or inborn error of metabolism In the main this relates to formation of uro- or uro-type porphyrins and it is questionable whether the term porphyria ought to be applied at all unless these can be demonstrated The cases of idiopathic coproporphyrinuria to be discussed subsequently also may represent constitutional metabolic errors but at the present time the evidence on this point is inadequate It is also uncertain whether the appearance of uro type porphyrins with or without porphobilinogen may occasionally be secondary to a disease other than porphyria Both substances have been observed in association with such widely variant diseases as cirrhosis and systemic sporotrichosis[16] but whether these were precipitating factors in individuals with latent (constitutional) porphyria is not known This would appear logical in view of the rarity of such occurrence

In cases of porphyria the amounts occurring in the urine often are sufficient to account for gross changes in color at least changes in color after exposure to light In any event the increase in porphyrin in this group is sufficient so that spectroscopic demonstration usually is easy Gunther preferred the term porphyria to porphyrinuria because the feces often contain more porphyrin than the urine This term seems even more justified in view of van den Bergh s case[18] of porphyrinemia without porphyrinuria here again the feces contained large amounts of porphyrin

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The older classifications of porphyria largely followed the work of Gunther who divided the disease into three types, 1) congenital characterized by light sensitivity, 2) acute, characterized by abdominal or nervous manifestations and 3) chronic, in which light sensitivity was associated with abdominal and/or nervous symptoms. Waldenstrom designated the latter as "cutanea tarda" because of the usually late appearance of the skin lesions in these cases[121]. Attempts have been made to classify the disease on a purely chemical basis[12,13], depending on whether type I or type III porphyrins are excreted, but this is scarcely warranted. Nevertheless, as noted in the following, there are rather consistent chemical differences between the various forms.

It is believed desirable to abandon the term congenital, as it probably relates with equal importance to nearly all cases whether the symptoms are cutaneous, abdominal, nervous or a mixture. Furthermore it is believed preferable to qualify the term acute by the word intermittent, since this applies so well to a great majority of the cases in which acute episodes of pain or nervous aberration are characteristic. Finally, it would appear most reasonable to substitute the term "mixed" for the "chronic" type of Gunther, since this most aptly describes in a single case the concurrence of manifestations of the two main forms. However, it should be emphasized that the term "mixed" is used in a clinical sense only, and in fact it is believed that the photosensitive type differs fundamentally (see Pathogenesis). With these considerations the following classification is regarded as most suitable.

Intermittent Acute Porphyria

Gunther[8] and subsequent investigators[14] divided acute porphyria into a "toxic" and an "idiopathic" form. It is doubtful whether they are fundamentally different, and, as mentioned previously, there is evidence[113] that substances such as sulfonal or trional are merely precipitating factors. This is in accord with Gunther's concept that in such individuals, usually females, a constitutional anomaly exists which predisposes to porphyria.

Mason and his associates[14] collected 100 cases of acute "toxic" porphyria from the literature prior to 1933. Of these 68 had used sulfonal, 11 trional. More than 90 per cent of the cases were in women in the fourth to the sixth decades. Gunther introduced the term "porphyrismus" to

TABLE III

CLASSIFICATION AND DIFFERENTIAL FEATURES OF THE VARIOUS FORMS OF PORPHYRIA

1 *Intermittent acute type*	2 *Photosensitive type* Porphyria erythropoietica	3 *Mixed type* (Porphyria hepatica)
More common in females (about 1)	More common in males (about 1)	No sex preponderance
Onset of attacks usually in 3rd and 5th decades rarely earlier	Onset usually in infancy or early childhood	Onset usually in 4th 6th decades may be intermittent
Abdominal and/or nervous manifestations Hypertension frequently Melanosis of skin may be present without light sensitivity	Cutaneous manifestations usually hydroa aestivale seu vacciniforme solar eczema or dermatitis at times Erythrodontia common Splenomegaly and anemia in some cases usually after the disease has been manifest for several years	Cutanea tarda Mixture in varying proportion of manifestations given under 1 and
Urine contains porphobilinogen[133] porphobilin and Waldenstrom's porphyrin latter mainly as zinc complex usually with an excess of coproporphyrin III	Urine contains uroporphyrin I principally in the free form Porphobilinogen absent	Skin lesions often result from heat and trauma in addition to light peculiar purplish facies in some cases[1 8] Liver functional impairment or cirrhosis is relatively common Porphobilinogen is present only in association with abdominal pain or nervous manifestations not correlated with skin lesions Methyl ester of uro type porphyrin often exhibits melting point intermediate between that of uroporphyrin I (84 C) and that of the Waldenstrom porphyrin (258 260 C)

describe this abnormal constitution The very low incidence of the affection in individuals habitually taking sulfonal, likewise the inconsistency with which sulfonal produces porphyrinuria in animals appear to support his view The fact that the ingestion of various other substances notably lead, arsenic, safranin, luminal, veronal, sedormid and phanodorm occasionally has preceded an outspoken acute porphyria[33] suggests that patients classified in the 'idiopathic" group may have taken some substance of unrecognized importance In one of our cases an acute attack occurred after use of an ergot preparation as an abortifacient

Even alcohol is undoubtedly of significance in precipitating attacks in latent cases of porphyria Thus, in a series of 5 cases, alcohol, administered under close observation in the hospital resulted in very significant increases of uro- and copro porphyrin and porphobilinogen excretion in 4, in one of these abdominal pain and nervousness were aggravated In the fifth case no effect was observed This was an example of isolated porphobilinogenuria without increased urinary porphyrins

It should not be assumed that barbiturate invariably precipitates an attack A patient, who had been seen in previous typical attacks of porphyria, was studied again during a complete remission this time because of active pulmonary tuberculosis After some time in the hospital without any symptoms of porphyria it was found that she had been receiving phenobarbital several times daily for a considerable period

In recent years intermittent acute porphyria undoubtedly has been recognized with much greater frequency than prior to 1933 Mason and associates in that year were able to collect but 46 cases of the idiopathic type from the literature In 1937 Waldenstrom reported 143 cases which he had studied in Sweden These included both the so-called toxic and idiopathic types Many cases have been recorded in the intervening period[13, 13, 141] Since 1934 we have had opportunity to study the protocols and urines of 83 cases of porphyria of all types of which 38 cases were studied in Minneapolis Of this group 56 were classified as intermittent acute in type, 13 were entirely latent, without history of attacks or of photosensitivity, all of these were members of families of one of the intermittent acute or mixed cases, 5 were of the photosensitive and 9 of the mixed type

The frequently familial incidence of the intermittent acute form has only been recognized in recent years, the delay in this regard undoubt

edly being due to the fact that in many instances members of the family of the presenting case have the disease only in its latent form Careful examination of the urine however often will reveal small amounts of porphobilinogen or Waldenstrom porphyrin or both The amounts of the latter may be so small as to require suitable concentration on talc[17]

Gunther believed that acute porphyria was limited in occurrence to individuals of a neuropathic constitution Several of his cases had either given a history of previous nervous disturbances or these had been noted in immediate members of the family The family reported by Barker and Estes[10] was the first remarkable example of familial incidence Two sisters in this family died of the disease a third had typical manifestations while both the mother and the grandmother on the maternal side gave a history of attacks of colic constipation vomiting and dark urine

The family shown in Fig 4 reveals the manner in which latent cases might be overlooked

Symptoms and Physical Findings —The chief symptoms and physical findings of intermittent acute porphyria are referable to the abdomen and the nervous system Severe *abdominal pain* of colicky type is commonly one of the first symptoms Often this is in the lower abdomen at least at the outset but may become generalized *Nausea* and *vomiting* usually are present and frequently severe In spite of the severe abdominal colic muscle spasm usually is absent and the abdomen is soft [8] *Constipation* nearly always is a prominent symptom and may be extreme in degree in one of Gunther s cases there were no feces in the rectum for a period of ten days Roth[1] reported an exceptional case in which diarrhea was present throughout the course of the illness

Mild *jaundice* is observed rarely This is to be distinguished from another type of *skin pigmentation*, which is not uncommon and which may be of a diffuse yellowish brown nature most marked on face and abdomen or it may take the form of freckle or chloasma like spots particularly on the face Darkening of the hair is observed often In some instances the development of pigmentation may precede even for years the onset of acute porphyria During the attack the pigmentation may increase rapidly[18] Nothing certain is known as to the origin of the pigment The mucous membranes are not pigmented and no evidence of adrenal insufficiency has been found[16]

Hypertension is frequent In 30 of the cases studied in Minneapolis,

in which data were available, elevations of the systolic pressure above 140 and/or the diastolic pressure above 90 were observed in 17 The blood pressure may be markedly elevated during the acute episode, only to return to normal during the remission Retinal arteriolar spasm may be present and disappear synchronously Tachycardia is observed fre

Familial Occurrence of Porphyria

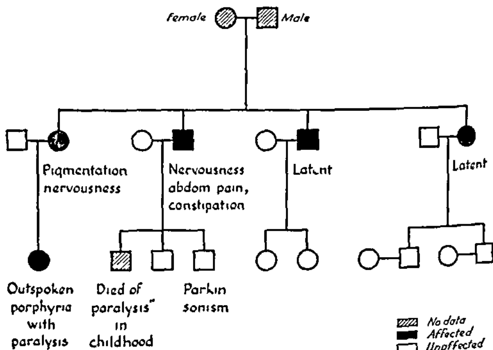


FIG 4 Familial occurrence of porphyria All of the cases labeled as affected exhibited porphobilinogen or a uro type porphyrin or both in the urine

quently and electrocardiographic changes have been reported[1 9] These manifestations together with the *weak, hoarse voice* which at times is noted are probably due to vagus paresis but whether due to central or peripheral involvement has not been determined That changes in the brain and spinal cord may occur has been established[130]

The *mortality* of acute porphyria has generally been regarded to be very high principally because of the frequent involvement of the nervous system which is mainly responsible for death It should be borne in mind, however that milder cases recovering from the disease probably

have not been recognized in many instances Many of our cases are living and in relatively good health, and we have become somewhat more optimistic about the *prognosis* The actual cause of death most often is a respiratory paralysis usually preceded by marked weakness of the extremities or often by a complete flaccid quadriplegia This is more often not symmetric and ascending in its development and hence as Waldenstrom points out, usually may be distinguished from the typical Landry paralysis Nevertheless all cases of the latter type should be investigated carefully with the possibility of porphyria in mind

The symptoms of paralysis usually are preceded by a variable period of nervousness insomnia irritability indefinite discomfort such as aching and in some instances actual pain in the extremities *Sensory disturbances* such as hypaesthesias to light touch or pain and also paraesthesias may be complained of These often persist for a few days or even weeks before the appearance of further symptoms In most cases there is next a sudden onslaught of severe colicky pain in the abdomen such as has been described already During this period usually of to 3 weeks duration the patient may be *irrational* or present *hysterical behavior* Visual and auditory *hallucinations* are at times prominent noisy *delirium* may alternate with marked *apathy* The frequent occurrence of other *psychopathic phenomena* such as maniacal or severe depressive states or epileptiform attacks further influenced Gunther in the belief that a constitutional inferiority exists in these cases In the late stage of acute porphyria signs of *bulbar palsy* such as dysphagia and dysarthria are common complete loss of ability to swallow or to articulate may result *Ocular palsies* are observed at times and *amaurosis* due to optic neuritis has been reported *Respiratory paralysis* is common When a *remission* occurs as it commonly does the improvement may be dramatic Patients who were completely paralyzed in all four extremities and bedridden for months may be able to walk again and even resume their normal activities to a surprising degree Residual contractures of the hands are not uncommon In a few of the milder cases an apparent complete recovery has been observed but in the majority the urine usually continues to exhibit small amounts of either porphobilinogen or Waldenstrom porphyrin or both In many cases the attacks have been recurrent over a period of months or even years Long remissions however are not infrequent

Diagnosis — The diagnosis of acute porphyria depends chiefly upon a careful examination of the urine with the thought of the disease in

mind. It is important to re-emphasize that the urine is not always red, if only chromogens are excreted, the red or dark brown color first appears after exposure of the urine to light, sunlight being most effective. The period of light exposure necessary to development of the red brown color varies from a few minutes to several hours. Waldenstrom and Vahlquist[131] reported that porphobilinogen is parent not only to the porphyrin but also to a dark brown pigment of nonporphyrin character which they designated porphobilin and which probably is synonymous with the "urofuscin" of the earlier literature. This substance is responsible for the dark brown, sometimes almost black, color of the urines of intermittent acute porphyria cases and possibly may be related to the skin pigmentation. It exhibits spectroscopic absorption in the same region as urobilin or stercobilin, although more diffuse and extending down in the blue from 500 mμ. Unlike urobilin, it does not exhibit green fluorescence with zinc and in fact its zinc complex is insoluble. Waldenstrom and co-workers obtained some evidence that it is a chain polymer of dipyrrylmethenes. They stated that the conversion of porphobilinogen to porphobilin was promoted by heating in alkaline solution and to porphyrin by heating in hydrochloric acid solution.

Porphobilinogen exhibits an Ehrlich aldehyde reaction[31, 111]. Unlike that of urobilinogen the aldehyde compound is insoluble in chloroform[31], this constitutes, therefore, a simple and valuable test for the diagnosis of porphyria, with which false positive reactions have been shown to be very rare[134]. It may be noted also that porphobilinogen is insolube in petroleum ether[31, 121], hence it does not interfere in the quantitative determination of urobilinogen in the urine or feces. Porphobilinogen has not been demonstrated in the bile or feces, although Prunty[136] found it in large amount in the liver in a case of porphyria.

Recent studies by Hawkinson[137] in this laboratory have shown that porphobilinogen is regularly accompanied by another chromogen which differs in not exhibiting an Ehrlich aldehyde reaction. This substance may be separated from porphobilinogen on the basis of differing solubility characteristics. It is readily converted to a uro-type porphyrin by means of irradiation or heat. The occurrence of this chromogen in association with porphobilinogen has not been recognized in the past, and this raises the question as to whether porphobilinogen is actually a porphyrin precursor, as has been believed[131].

The *abdominal manifestations* of acute porphyria have often been misleading in the *differential diagnosis*, laparotomies have been per-

formed in a number of cases with preoperative diagnosis of appendicitis bowel obstruction gall bladder disease or gall stones The possibility of confusion in diagnosis is enhanced by the occurrence in some cases of fever and neutrophilic leukocytosis Temperature often is higher than normal and rarely higher than 100 to 102 F The leukocyte count is at times elevated to from 15 000 to 20 000 with 80 to 95 per cent polymorphonuclear cells but more often it is normal Of genuine importance in the differential diagnosis is the presence of a soft abdomen in association with Gunther s triad of symptoms i e abdominal colic vomiting and severe constipation[8] Gastrointestinal x ray examination often reveals areas of marked and persistent bowel spasm particularly in the ileum In other localities notably the stomach and colon dilatation is observed more commonly When in addition to these symptoms and findings, evidence of peripheral neuritis develops the clinical picture of acute porphyria is reasonably complete and confirmation of the diagnosis then depends upon the urinary findings

Weakness nervousness and tachycardia in cases of porphyria may lead to an incorrect diagnosis of hyperthyroidism or weakness and pigmentation to the consideration of Addison s disease One of our cases first had an appendectomy because of abdominal pain a year later a thyroidectomy for weakness and nervousness at a still later period treatment with salt and cortical extract because of a diagnosis of adrenal insufficiency Neither this treatment nor the previous operations had in any way improved her status Porphyria was first suspected when she developed a flaccid quadriplegia

Photosensitive Porphyria

This type of porphyria occurs much less frequently than the acute form of the disease We have had opportunity to study but two cases in seventeen years and we have been aware of but five additional cases in the United States during this period Turner and Obermayer[140] found 86 cases reported in the literature prior to 1936 but some of these undoubtedly were of mixed type The disease displays a sex incidence quite the opposite to that noted for acute porphyria being distinctly more common in males Thus of 82 cases 56 were males 6 females[14] Two or more siblings in a family repeatedly have been observed to have the disease[8, 140] hereditary transmission has been mentioned but rarely Garrod[14] included the disease among his inborn errors of metabolism

and regarded its transmission as a regressive characteristic. In a few instances consanguinity in the parents has been recorded. The age at which symptoms are first noted is variable. Red urine and light sensitivity may be observed from birth, in fact Mason and his associates[14] mention a stillborn infant, whose bones were deeply pigmented and red brown in color. Turner and Obermayer classify 7 of the 86 reported cases as having begun in very early fetal life. This was based upon Macl ey and Garrod's statement[143] that erythrodontia is evidence of such an early beginning of the disease.

With rare exception the earliest sign of photosensitive porphyria is the *red color of the urine*. This usually precedes the appearance of skin lesions by an interval varying from weeks to years. The intensity of the wine red or at times brownish red color of the urine also varies considerably, in some instances the porphyrinuria is intermittent. In patients having recurrent attacks of hydroa aestivale the onset frequently is noted in the early summer months when the sun's rays have become more intense. While the majority of cases of photosensitive porphyria exhibit porphyrinuria without relation to season of the year, occasional cases have shown seasonal variation in this respect as well. In fact the first patient, in whom the simultaneous occurrence of hydroa and porphyrinuria was noted[144], related that the urine was normal in color except during the attacks of hydroa and that the latter rarely occurred except in the summer time. In by far the majority of the cases reported subsequently however the red urine has been a more constant symptom. In certain instances the mother has stated that both urine and feces were red from the time of birth.

The *sensitivity to light* in this form of the disease is manifested by the appearance of *skin lesions*, which are of the type first described by Bazin under the name "*hydroa vacciniforme*". The term "*hydroa aestivale*" has been widely used synonymously. In spite of attempts to distinguish these conditions a sharp dividing line does not appear to exist and as Gunther emphasized they are symptoms rather than entities. For a number of years, until Anderson's report in 1898[144] the association of hydroa aestivale with porphyrinuria passed unrecognized. Linser[145] was the first to point out that this was more than a casual association. While it has been shown that some cases of hydroa aestivale never exhibit porphyria and are causally unrelated it is likely that the relationship has escaped notice in many instances, even since Anderson's report, because of failure to examine the urine spectroscopically.

According to Gunther[8] attacks of hydroa aestivale recur at least annually most often beginning in the spring then persisting throughout the summer, unless particular care is taken to avoid the sun's rays The first symptoms of the attack consist of itching burning or other sensation of irritation of the exposed surfaces of the skin frequently associated with photophobia and often an outspoken but not suppurative conjunctivitis At times diffuse hyperemia and edema of the face is noted within a few hours after exposure to light *Systemic symptoms* such as malaise nausea and headache may be observed A *vesicular* or *bullous eruption* the principal constituent of *hydroa vacciniforme appears on the face* and backs of the hands or other considerably exposed areas Gunther points out that the ears are particularly involved while the region of the mouth and chin remains relatively free The vesicles contain a serous fluid which at times becomes purulent because of secondary infection if uncomplicated a crust forms over the lesions and healing occurs with relatively little although definite scarring Secondarily infected bullae often ulcerate and are responsible for *marked scarring* and *deformity* The scars usually become pigmented In the late stages of the disease *after years of repeated attacks, extensive mutilation of the face and* hands results (see Fig 5) The tip of the nose as well as the alae nasae also the ears are particularly likely to exhibit defects Contractures of the cheeks and lips because of scarring lesions may bring the upper teeth into prominence The teeth at times are colored a dark reddish brown or even pink a phenomenon spoken of as *erythrodontia*[118]

Extensive *ocular damage* may result because of scarring and deformity of the lids conjunctivae and corneae The lid slits often are narrowed although in some cases moderate ectropion may be noted Varying disturbance of vision has followed these processes

Deformities of the fingers often are marked in the late stages of photosensitive porphyria Swelling is common in the eruptive periods of the disease The terminal phalanges are involved most severely The finger nails commonly exhibit abnormalities consisting of reduction in size longitudinal ridging or other rough irregularities The nails may be lost during attacks of hydroa only to return and then be lost again in subsequent attacks[8] The finger nails at times are a dark red in color

A generalized increase in *skin pigmentation* is not uncommon This may be accompanied by *hypertrichosis*[7 8 33 1 4 1 3 140] A slightly yellowish pigmentation of the conjunctivae has been noted which may have been due simply to bilirubin since moderate increases in serum bilirubin have been recorded

In the *differential diagnosis* of photosensitive porphyria the skin lesions cannot be regarded as pathognomonic. The extensive lesions of the face at times have resembled those of lupus vulgaris and of leprosy[8]. Xeroderma pigmentosum may be strikingly similar. In other cases a more diffuse thickening of the skin, simulating scleroderma, has been reported[140]. The lack of increase of porphyrin in the urine does not always exclude porphyria. This was evident in van den Bergh's case[48] in which coproporphyrin was present in the blood, bile and feces in



FIG 5. Gunther's case of congenital porphyria (Petry). From p. 666, Die Krankheiten des Blutes und der blutbildenden Organe, edited by A. Schittenhelm, Julius Springer, Berlin, 1925.

relatively large amounts, while the concentration in the urine was said not to be increased.

According to Turner and Obermayer[140] about 200 cases of hydroa aestivale were reported up to 1938 and of these about 86 exhibited porphyria. The skin lesions usually were more severe in the latter group. There is little doubt that other as yet unknown substances are photosensitizing to certain individuals, who do not have porphyria, but who are afflicted with various "solar dermatoses", such as hydroa vacciniforme. On the other hand porphyrins have been believed to be the cause

of light sensitivity in certain instances of solar eczema[147] In distinguishing porphyria from other causes of hydroa aestivale attention should be given *to the wave length of the light productive of skin lesions In cases* of porphyria it is probable that the light most effective in the production of hydroa is of wave length 3 100 to 4 500Å particularly 4 000 Å *corresponding closely with the ultraviolet absorption of the natural porphyrins*[148] Little or no effect is obtained following exposure to radiant energy of less than 3 200Å Thus if ordinary window glass consistently serves to protect an area of skin repeatedly exposed to the summer sun porphyria may be excluded with considerable certainty Some years ago a girl of 14 was studied who had very typical attacks of hydroa aestivale but whose urine feces and blood serum repeatedly failed to show any evidence of porphyria Vesicles appeared only after exposure to unfiltered sunlight but if direct sunlight were filtered through ordinary window glass the skin remained unaffected Further studies revealed that the light of importance in this instance was shorter than 3 200 A This patient in fact was shown to have an abnormal substance of unknown character in the blood serum with absorption at 2 900 Å

Although porphyrins unquestionably are photosensitizing substances some question exists about their exact relationship to the pathogenesis of hydroa aestivale Blum and coworkers[148, 149] reported failure to produce *the characteristic vesicles by exposing areas of the skin of a con*genital porphyrinic to light of wave length corresponding to the ultraviolet absorption of the porphyrins The patient previously had had spontaneous hydroa lesions on the exposed parts of the body In the experiments reported previously unexposed areas of skin were the only ones tested The same observations recently have been made in a case studied in this laboratory[189] it was impossible to produce vesicles by means of artificial ultraviolet light but exposure to sunlight for periods insufficient to produce sunburn resulted in vesicle formation The results of the experiment which Strauch[60] carried out in a child suggest that repeated or chronic exposure is required at least in some cases The first injection of porphyrin with subsequent exposure to sunlight resulted in erythema only one week later the same amount was injected and the *duration of exposure to sunlight was somewhat lessened* in spite of this the reaction was much more severe with marked vesicle formation

Splenomegaly is not uncommon in cases of photosensitive porphyria *Rarely the spleen attains the large size characteristic of other diseases of* the splenic anemia group Confusion with this group of diseases may occur inasmuch as anemia is also encountered frequently The exam

mination of the urine blood serum and feces for porphyrin again is of decisive value Mackey and Garrod[143] collected considerable data as regards splenic enlargement and state that it has not been observed in young children who are afflicted with the disease, but regularly appears as time goes on, in their case the spleen was not palpable at the age of 6 but at 8½ reached three inches below the rib margin in the left nipple line Nevertheless we have recently observed a child of four, with typical photosensitive porphyria, having marked splenomegaly and severe hemolytic anemia[180] Splenectomy was followed by disappearance of both photosensitivity and anemia Mackey and Garrod[143] concluded that splenic enlargement was purely secondary They considered it probable that in course of time the spleen becomes enlarged in all cases of congenital (photosensitive) porphyria The liver may be enlarged, in the case Petry it did not extend below the costal margin[9] In the four year old girl just mentioned the liver edge was palpable 3 cm below the rib margin in the mid clavicular line

Anemia often is associated with signs of abnormal bone marrow activity Normoblasts erythroblasts, megaloblasts( ) and at times erythrophagocytosis have been observed in the peripheral blood[143] Late in the course of the disease the case Petry exhibited anemia very similar to pernicious anemia[8, 9] with hemoglobin 14 per cent, erythrocytes 920 000 per cu mm and leukocytes 3 000 per cu mm, poikilocytosis anisocytosis and basophilic stippling were prominent The blood serum contained increased bilirubin, which gave an indirect van den Bergh reaction Hematin also was demonstrated The bone marrow obtained at necropsy[9] was said to be megaloblastic but the illustration of these cells in Borst and Konigsdorffer's monograph[9] is much more suggestive of normoblasts or erythroblasts and the possibility of a chronic hemolytic anemia does not appear to have been excluded

The examination of the *urine* obviously is of paramount importance in these cases The urine is strongly acid in reaction This is true as well in acute porphyria The typical *color* varies from light red through Burgundy red to a dark reddish brown Urobilin rarely is increased sufficiently to aid in composing the color of the urine The Ehrlich reaction for porphobilinogen is negative in this type of porphyria Consequently the dark brown or almost black color due to porphobilin and observed so often in acute porphyria, is not seen The uro- and copro-porphyrin I are excreted in the free state rather than as the zinc complex observed in the intermittent acute form

Although the amount of porphyrin in the urine may fluctuate

markedly in some cases in others it remains relatively constant for long periods as in the case Petry who excreted from 0 3 to 0 5 gm daily on repeated examinations over a three year period[8] Both urine and feces contain coproporphyrin in markedly increased amount Uroporphyrin thus far has been demonstrated in the feces of but one case (to be published) of the photosensitive type[100] in a previous case it was not found in the feces[1 5]

Mixed Porphyria

This corresponds with what Gunther[1 5] called chronic porphyria and what Waldenstrom[111] terms the cutanea tarda type This term has much in its favor but it is believed preferable to use the simpler designation 'mixed at least until a more specific name based on etiology or pathogenesis can be chosen In this connection another possibility will be discussed now

The mixed or cutanea tarda form presents cutaneous together with abdominal and/or nervous manifestations in varying degree Certain cases have been observed recently in which the only complaints were cutaneous in nature Vesicle formation in this form often follows heat or trauma as well as light exposure Nevertheless in our experience the lesions have been restricted almost without exception to the areas of skin exposed to light Abdominal pain or nervous disturbances described for the acute form are likely also to be intermittent in this type but in general appear not to be as severe Liver functional impairment is common Jaundice ascites and even outspoken cirrhosis may be present The hepatic aspects of this form have been emphasized recently by Brunsting and co-workers[11] and Schmid s studies[107] in this laboratory indicate that the liver in these cases as contrasted with the infantile photosensitive form probably is the site of abnormal porphyrin formation

The urinary findings in the mixed form also are intermediate between those of the photosensitive and the intermittent acute forms Porphobilinogen has been observed only in relation to the presence of abdominal or nervous symptoms It may be noted in association with uroporphyrin I although the ester melting point is often somewhat lower than in the pure photosensitive group from 270 to 280 C rather 284 to 86 C The reason for this has not been determined but it may

well explain the previous reports of the occurrence of uroporphyrin I in acute cases[14, 138] or of uroporphyrin III in photosensitive[139] cases

PATHOGENESIS

This is not well understood but a number of facts recently have become clear which throw considerable light on the problem The absence of porphobilinogen in cases of the infantile or "congenital" photosensitive form and its regular presence in association with abdominal or nervous symptoms point to it as the substance to which the latter are in some way fundamentally related Conversely, it has not been possible to correlate excretion or serum content of porphyrin itself with these manifestations Photosensitivity, however appears to be related to porphyrin rather than porphobilinogen Free uroporphyrin I evidently is most important in this respect though its zinc complex probably is photosensitizing to a lesser degree Thus in certain 'mixed' cases with moderate light sensitivity all of the porphyrin demonstrable in the urine was in the form of metal complex of course this does not prove that it existed in this form before entering the urine Another important possibility is that the greater the admixture of the '208" or hepta carboxyl (type III) porphyrin with uroporphyrin I the lesser the photosensitizing activity In the "pure photosensitive form the uroporphyrin I excreted is quite pure (ester M P 284 C) while in the intermittent acute form without light sensitivity, the Waldenstrom porphyrin, which incorporates a fair amount of the 208 porphyrin melts as a rule at 258 to 260 C In the mixed' cases with less severe photosensitivity the melting point frequently is noted between 270 to 280 C

More important as regards pathogenesis are the recent studies of Schmid[167], which reveal that in the intermittent acute and 'mixed" type the liver contains large amounts of porphyrin while no significant increase is exhibited in the bone marrow or peripheral erythrocytes, conversely in the photosensitive form both the developing and circulating erythrocytes exhibit large amounts of porphyrin as compared with the liver These findings contrasted with the prominent evidence of liver involvement in the former group and of bone marrow hyperplasia splenomegaly and hemolytic anemia in the latter suggest a much more fundamental classification based on pathogenesis as follows

Type

1. Porphyria erythropoietica (photosensitive or porphyria congenita)
2. Porphyria hepatica
   a. Mixed or cutanea tarda
   b. Intermittent acute

Further study is needed before this classification can be accepted with finality but present information indicates that it is entirely reasonable if some reservation is made as to inclusion of the intermittent acute type under porphyria hepatica While it is clear that the liver in this form often contains large amounts of porphyrin and/or porphobilinogen evidence of hepatic disease often is not seen either clinically or at necropsy and the possibility exists that the nervous system itself is an important site of porphyrin formation at least in the cases in which also nervous manifestations are prominent

IDIOPATHIC COPROPORPHYRINURIA

There are certain individuals with or without symptoms in whom excessive excretion of coproporphyrin III is observed The most striking have been two adult males one white and one negro without symptoms who were found to excrete large amounts of coproporphyrin III in the urine bile and feces[9] The first of these was encountered during a survey of presumably normal personnel the second had recently had uncomplicated diphtheria and was studied because of recent reports of production of coproporphyrin III by diphtheria bacilli[151 1] The excessive excretion in this second case was not believed related to the diphtheria however as it persisted until the patient a transient was last seen several months after the diphtheria These two cases appeared to be entirely similar in that large amounts of coproporphyrin III were being formed and excreted on an unknown basis The amount in the urine ranged from 2 to 5 mgm per day that in the feces from 30 to 60 Mg Porphyrin could not be demonstrated in the blood in either instance These cases appear to differ from another group that must also be designated as idiopathic coproporphyrinuria in which however the amounts excreted are much smaller usually ranging from 300 to 1 500 mgm UCP per day with 50 to 80 per cent type III Rather paradoxically these patients have symptoms particularly abdominal pain and constipation but in some instances mild nervous manifestations as well

In one case, which appeared to fall in this group and which was studied over a period of several years, it was discovered eventually that the patient was a barbiturate addict. It has not been possible to determine, however, whether the addiction was the cause or the result of the increased porphyrin excretion. The possibility certainly exists that this case and others of the same group are due to unrecognized chemical toxicity. For the time being at least it appears best not to designate these cases as porphyria, since there is no evidence of an inborn error of metabolism. In no instance has any familial tendency been observed, although it has been sought with regularity.

Kammerer[13] described a case of the latter type, characterized by marked abdominal pain, and in this instance it was believed that the coproporphyrin in the urine was derived from hemoglobin in the intestinal tract. Kammerer stated that the porphyrin diminished and the symptoms abated on a 'porphyrin poor" diet, i.e. one omitting meat and green vegetables, also that exacerbation occurred when meat was added in plentiful amount. We have used Kammerer's diets in two of our cases of the above mentioned group but have not been able to correlate symptoms or changes in porphyrin excretion with changes in the diet.

Therapy of Porphyria

Except for protection from the light in cases of photosensitive porphyria specific therapy is unknown. To avoid the effects of light ordinary measures such as dark glasses, umbrellas and gloves are of considerable aid. Remaining indoors except on cloudy days, is distinctly safer. Gunther recommends that these individuals should obtain night employment so that they may sleep in a darkened room during the brightest hours of the day. The possible value of light absorbing ointments or applications to the skin has not been studied adequately.

If there is any evidence of heightened blood destruction or increased erythropoiesis, especially if associated with splenic enlargement splenectomy is believed to be indicated on the basis of the remarkable results which have been referred to already in one of our cases[190].

In intermittent acute porphyria with abdominal or nervous manifestations an effort should be made first of all to discover and remove any substance of possible etiological importance such as sulfonal, trional or barbiturate which the patient may have been ingesting. Other measures which may then be employed and which are probably of

equal value in the idiopathic group include warm baths to aid in relaxation of intestinal spasm and warm saline enemas for the same purpose and to aid in overcoming constipation Demerol in doses of 50 to 100 mgm subcutaneously has been of some help in allaying pain in the abdomen or extremities although the relief usually has not lasted above four hours Recently methodon (dolophine) in amounts of 10 to 15 mgm by mouth has been about equally effective According to Gunther sleeplessness should be treated with chloral hydrate or morphine while all barbiturates are to be avoided Good results have been reported in acute porphyria following liver extract therapy Our own experience with it however has not been convincing in one case a relapse occurred while liver extract was being given Turner and Obermayer[190] found no benefit from liver extract in a case of photosensitive porphyria

Folic acid recently has been recommended[191, 192] to bring about remission in acute porphyria but our own experience with it has only been disappointing The same has been true in several cases in which large amounts of vitamin B_1 have been given either alone or together with folic acid Stich[193, 194] very recently has reported that porphyria responds to riboflavin in doses of o to 40 mgm daily but he does not give protocols which permit one to assess his results The results with this method in two of our own cases have been disappointing

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CHAPTER X

RICKETS

By EDWARD S MILLS

TABLE OF CONTENTS

Etiology

The isolation of vitamin D from cod liver oil and radiated sterols and the demonstration that it will both prevent and cure rickets have explained many interesting observations concerning the etiology of the disease

Rickets has long been recognized as part of the price paid by humanity for civilization It does not occur in animals except when they are transferred from their natural environment and is rare among races who live close to nature Savages may starve and may become the victims of pestilence but they do not suffer from rickets Hence the disease is almost unknown in native parts of Africa is rare in China and Japan but affects from 30 to 90 per cent of infants from the poorer districts of many European and American cities It is rare in subarctic regions, in the tropics and at high altitudes Greenland Iceland Norway, and Denmark are almost free from the disease as are Greece Turkey and Southern Italy In 1912 Still reported that the disease was prevalent in Australia South Africa and South America It is thus evident that countries where sunlight is abundant or where the diet is rich in fish oils escape

Race Race appears to have little bearing on the incidence of the disease The negro in his native state is immune although unusually susceptible when introduced to civilization Eskimos due to their diet rarely contract the disease Eastern races are susceptible if deprived of sunlight as in the slums of large cities

Climate and Season Schmorl[13] showed that rickets may begin at any time but that the highest percentage of early manifestations of the disease is between November and May The percentage of cases with signs of healing on the other hand increased during summer and reached the highest peak during the autumn after which it fell again as winter came The higher incidence of the disease in winter depends upon the sun s low altitude When the latter is below 35 the anti rachitic effect of sunlight is negligible due to the effect of the thick layer of atmosphere through which it must pass in filtering out the ultraviolet rays Thus cities such as London and Glasgow where the sun s altitude is less than 35° for at least five months in the year have a high incidence of rickets[62] Smoke and other impurities in the atmos phere further inhibit the penetration of the antirachitic rays in these large cities On the other hand, on the island of Jamaica where the sun s highest altitude is never less than 50° rickets is almost unknown

Introduction

Synonyms Rachitis, rachitismus, morbus anglicus, die englische Krankheit

Definition A constitutional disease due to a deficiency of vitamin D, characterized by a disturbed mineral metabolism, an impaired nutrition of the entire body, and alterations in the growing bones

Historical In 1640 the Royal Society of London received so many reports from different districts in England indicating the appearance of a new disease that they appointed Glisson, Bates, and Rogenork to collect data and to report their findings In 1648 or 1649 Glisson published his treatise,[1] the first part of which is theoretical and original while the second part is practical and prepared from the notes of Bates and Rogenork The term rachitis was suggested by Glisson partly by the similarity of the sound to the common English word 'rickets,' derived from the old English verb wrikken, to twist awry, and partly from the Greek *ραχις*, the spine, for the reason that the dorsal spine was one of the first parts attacked

Shortly afterwards the disease was recognized on the Continent, where it was known as the morbus anglicus, under the erroneous supposition that it had originated in England Mayow of Oxford in 1660 (Comby) first called attention to the softening of the bones in rickets Boerhaave[3] in 1709 discussed it briefly in his aphorisms Syndenham gave an excellent description of the clinical features in 1711 About the same time van Swieten wrote extensively on the historical and pathological sides Guerin[4] and Trousseau[5] contributed to our knowledge of the pathogenesis of the disease

To Virchow belongs the credit for establishing rickets as an entity distinct from mollities ossium The monograph of Elsaesser on craniotabes, which appeared in 1843 established the fact that craniotabes is essentially of rachitic origin Broca[6] in 1852, according to Comby,[2] was the first to describe the histological lesions of the disease The names of Thomas Barlow[7] and of Cheadle[8] are as intimately associated with rickets as with infantile scurvy, and they are largely responsible for differentiating the two diseases The monograph of von Recklinghausen[9] which appeared in 1910 shortly after his death is a wonderful compilation of his own researches as well as those of others on the pathology of rickets The comprehensive review by Park[10] whose own investigations played no small part in clarifying many details of the problem, ushered in the modern concept of the disease

and Vogt[24] blamed the thymus, Stoeltzner and Salge[25] the adrenals and Hertoghe and Ausset[26] Claude and Rouillard and Hoennicke[27] the thyroid Experimental extirpation studies, Pappenheimer[28] and Rusca[29] later disproved these theories (3) The toxic action of various substances such as lactic acid Heitzmann[30] carbonic acid, Wachsmuth,[31] potassium phosphate Delcourt[32] volatile substances of confined air Kassowitz,[33] and intestinal poisons Spillmann[34] Charrin and Le Play[35] have been blamed at one time or another The acidosis theory of Pritchard[36] has withered also under the scorching rays of modern biochemical research[4] (4) There have been a number of bacterial theories of the disease One theory postulated a specific bacterium Chaumier[37] Hagenbach Burckhardt[38] while another merely claimed that the disease was a non specific infection Koch,[39] Morpurgo[40] (5) Guerin and Trousseau[5] were the first to recognize a faulty dietary as the cause of the disease Years later Cheadle[41] wrote rickets is produced as certainly by a rachitic diet as is scurvy by a scorbutic diet He recognized that the important factor was quality rather than quantity of food At this time it was well known that rickets was uncommon among breast fed infants but was frequent in those fed on cow s milk and other artificial foods These facts led to an investigation of the nature of the deficiencies in these diets as a result of which it became known that farinaceous foods have little or no antirachitic properties Then Cooper suggested that rickets was due to a faulty absorption of calcium following which Chossat Milne Edwards[4] Voit[43] and Baginsky[44] reported experimental rickets in animals deprived of earthy salts in particular calcium and phosphorus but Vierordt[4] was able to show that calcium absorption is normal in the disease Moreover Cheadle pointed out that rickets is very common in limestone cities in England in which the water is charged with calcium and also that farinaceous foods though rich in calcium and phosphorus are poor in antirachitic factors (6) Fat protein deficiency theory An analysis of rachitic foods as a rule shows a deficiency in fat and protein hence the theory that deficiency of these was the cause of the disease Moreover cod liver oil had been used from time immemorial as a folk remedy on the coast of England Holland and France and was introduced into France as a specific for rickets by Bretonneau of Tours Trousseau When Bland Sutton[4] added milk cod liver oil and powdered bones to the lean meat dietary of the animals of the London Zoo, a litter of lion cubs was reared for the first time in years, although signs of rickets had appeared already

Age. The majority of the cases of rickets occur between the third month and the third year. The disease rarely commences after the second year. Dunham, quoted by Park,[10] discovered a well advanced case in a prematurely born infant aged only one month and both Ylppo[14] and Hamilton[15] have noted that rickets makes its appearance earlier in prematurely born infants than in those born at term. Park found that this observation held regardless of whether the child was suckled or fed artificially. In explanation of these facts, it has been shown that the foetus accumulates over 80 per cent of its calcium stores during the last 3 months of intrauterine life. Rarely the disease may begin in intrauterine life and be well developed at birth, foetal rickets.

Overcrowding and Defective Hygiene. Although lack of exercise and defective hygiene have been stressed as causes of rickets, Findlay[16] and von Hansemann,[17] it now seems likely that these factors are of importance only in so far as they preclude sunlight.

Heredity. Ritter, Siegert,[18] and others have shown a higher incidence of rachitic children in mothers who themselves had rickets during infancy than in mothers who did not, but in the light of our present knowledge it seems likely that this was due to similar predisposing factors rather than to any familial tendency.

Influence of Associated Diseases. Parrot[19] maintained that rickets was simply a manifestation of congenital syphilis. Cannata[20] found that the incidence of congenital syphilis among 1,285 cases of rickets in Naples was 37.4 per cent. However, Cheadle[8] clarified the situation by pointing out that congenital syphilis modifies rickets but does not create it. Disorders of the gastrointestinal tract such as vomiting and diarrhea were claimed by Marfan[21] to play a role in the cause of rickets. It is conceivable that such disturbances could limit the absorption of vitamin D from the gut and thus predispose to the disease. Other predisposing causes listed by Marfan are latent or active tuberculosis, prolonged or repeated bronchopneumonia, especially that following pertussis, and chronic skin infections.

Historical Development of Conception of Cause of Rickets

Down the years prior to the discovery of vitamin D many theories were developed to explain why rickets occurred. Some of these deserve brief mention. (1) Pommer[22] and Tedeschi regarded rickets as a form of osseous dystrophy due to inadequate oxygen resulting from improper ventilation of houses. (2) Internal secretory theories. Basch[23] and Klose

day Twenty five years ago Buchholz[5] demonstrated cures of the disease as a result of the action of a gluhlicht which is an ordinary carbon filament electric globe It was only in 1919, however that Huldschinsky[3] showed that radiant energy in the form of ultraviolet rays from artificial sources possess a marked curative effect on rickets His observations were confirmed amply by Hess and Unger[54] Putzig[5] Karger[6] Sachs[57] Kramer, Casparis and Howland[8], and Chick and others[9] Hess, Pappenheimer, and Weinstock[60] were able to show that the most effective rays are about 300 millimicrons in length or shorter (300 millimicrons = 3 000 angstroms)

The next step forward came when Heilbron, Kamm, and Morton[61] Windaus[62] Hess[63] and Rosenheim and Webster[64] demonstrated that when certain of the sterols such as ergosterol and cholesterol in the impure state are subjected to the influence of ultraviolet rays they become powerfully antirachitic though inert in this respect when in the chemically pure state Thus it became clear that radiant energy whether from the sun or from artificial sources imparts to certain of the fatty constituents of food a powerful antirachitic factor An explanation of the production of the antirachitic factor by means of radiant energy on the skin effect of sunlight is afforded by the ingenious experiment of Hess A number of rats were divided into two groups and all were fed on rickets producing diet Each rat in one group was given one gram of skin daily To each rat in the second group the same amount of irradiated skin was given daily The rats in the first group developed rickets, but those in the second group did not Thus Hess showed that the effect of sunlight on the skin in preventing rickets is a simple photochemical reaction and not a complex biological process for the skin utilized had been excised before it was radiated Our present conception of the antirachitic factor is that it is a substance which develops in certain foodstuffs containing the higher sterols when they are exposed to radiation of special region - 500 to 3 000 angstroms, and secondly that it develops in the skin as a result of the same photochemical reaction It is now known as vitamin D

Physical and Chemical Characteristics of Vitamin D

At the present time no less than ten forms of vitamin D are known[10] but of these only two have a direct bearing on the cause and treatment of rickets Vitamin D_2 is obtained by irradiating ergosterol of plant origin Certain fungi such as mushrooms yeast and ergot are rich sources

Thus it came to be believed that the secret of the etiology of rickets was in some way bound up in the metabolism of fats.[7] These facts paved the way for the next theory, and when Mellanby[47] in 1919 announced that as a result of experimental observations, rickets could be considered as resulting from a deficiency of a fat-soluble vitamin, his experiments and conclusions were endorsed by the National Research Council. He called his substance vitamin A. This vitamin was found also to be the growth producing vitamin, a deficiency of which in young animals led to a type of ophthalmia known as keratomalacia.

Mellanby's announcement gave fresh impetus to the study of the disease, and out of an enormous literature on the subject certain facts, which did not jibe with his theory, came to be recognized. Briefly these are as follows: (a) That rickets tends to develop more readily when animals are confined to their cages than when they are allowed to run about in the open air, regardless of the diet. (b) That certain diets known to be deficient in vitamin A do not produce rickets, Sherman and Pappenheimer[48]. Shipley, Park, McCollum, and Simmonds[49] showed that the pathological condition induced by such diets was osteoporosis not rickets, and even suggested that vitamin A was not necessary for the full development of the disease. They were able to produce rickets by diets low in either calcium or phosphorus or both but failed if cod liver oil were added to these diets. (c) That certain oils (butter), though potent in fat-soluble A, are weakly antirachitic, while others (cocoanut oil), are antirachitic, though weak in the growth producing A. (d) Finally that the fat-soluble A in cod liver oil may be destroyed entirely by subjecting the oil to a temperature of 120° C for four hours in an atmosphere of oxygen without impairment of its antirachitic properties. It thus became evident that the antirachitic factor was distinct from vitamin A.

As long ago as 1890 it was recognized by Palm[50] that sunlight possessed a marked antiscorbutic influence. In 1912 Raczynski[51] wrote 'That it is the sun which plays the principal role in the etiology of rickets.' One of his experiments will serve as an illustration. Two puppies were suckled by the same mother at the same time. The one was reared in the sunlight, the other in the dark. The first developed normally. At the end of six weeks the second showed a diminution of the body calcium oxide and phosphorus pentoxide and developed rickets. His conclusion that the lack of the action of sunlight caused defective assimilation of calcium oxide and thereby rickets, cannot be refuted to

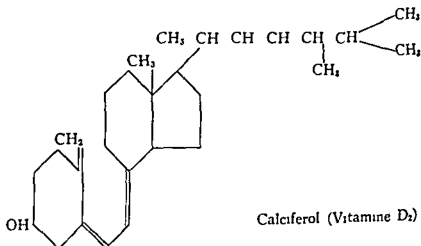
Morbid Anatomy

In order to understand the morbid changes which take place in rickets it is necessary to have a clear conception of what occurs normally at the growing end of a bone A section through the epiphyseal junction of a normal growing bone will show on the epiphyseal side a layer of resting hyaline cartilage beneath which is a layer of proliferating cartilage in which the cells are arranged in regular columns paralleling the long axis of the bone As these cells proliferate in a direction away from the diaphysis those cells nearest the latter undergo vacuolar degeneration Into the spaces left by the degeneration and disappearance of these cartilage cells there come capillaries and bone forming cells or *osteoblasts from the diaphysis* These are responsible for the deposition *of the bony matrix in which the mineral salts are deposited* According *to Shohl* and *Wolbach*[112] *the degenerating cartilage cells form* an *almost straight line across the epiphysis of the bone*

The first histological evidence of rickets is the cessation of the cartilaginous degeneration and the disappearance of the line of clear or empty cartilage cells As a consequence ingrowth of capillaries and osteoblasts is impossible At the same time due to survival of the cartilage cells on the diaphyseal side and active proliferation of the cartilage cells in the epiphysis the width of the cartilage increases Its epiphyseal border not infrequently presents a jagged or irregular appearance due to irregular attempts at cartilaginous degeneration and ingrowth of osteoblasts As this process progresses calcification of the cartilaginous matrix ceases entirely but osteoid material accumulates about the capillaries at the end of the diaphysis adjacent to the cartilage Due to the pressure of weight bearing this material frequently becomes moulded into transverse strata If the disease process continues both the cancellous bone of the diaphysis and the dense cortical bone are resorbed The entire bone thus becomes soft and pliable When vitamin D is given the first change is degeneration of the cartilage cells adjacent to the diaphysis Vascular penetration into these occurs within 48 hours bringing osteoblasts and thus permitting deposition of bone forming salts Thus is there produced the so called line test of healing However orderly regimentation of the cartilage cells is incomplete for a considerable period of time so that some evidence of the disease can be recognized for a long time by the expert pathologist The gross abnormalities of the bones such as occur in the skull, the ribs and the growing ends of the long bones can all be explained on the basis of these

During radiation the ergosterol yields four isomers, lumisterol, tachysterol, calciferol, and suprasterol Of these calciferol has the greatest antirachitic activity and the least toxic action It is now regarded as pure vitamin D_2 and can be isolated in crystalline form Its antirachitic activity is so powerful that 0 0.5 micrograms daily, one unit, will prevent the development of rickets in a rat receiving a rickets-producing diet

Vitamin D_3 is the one which develops in the skin under the action of ultra violet rays, and which is present in cod liver oil It has a slightly different formula from vitamin D , calciferol, and is known as activated 7 dehydrocholesterol It was first isolated by Windaus and his associates[109] in Germany from the sterol of hog skin Vitamin D^3 occurs



Calciferol (Vitamine D_2)

in nature in the liver oils of bony fishes and to a slight extent in egg yolk, butter cream, and milk It is of interest that the liver oil of the halibut has twelve times the potency of vitamin D as has that of the cod Vegetable oils such as cotton seed corn, or maize oil are inert in this respect unless artificially irradiated In general these vitamins are very stable to heat and oxidation They are soluble in the usual fat solvents but insoluble in water

The precise mode of action of the vitamin is unknown It would appear to aid the absorption of calcium and phosphorus from the bowel and to encourage their deposition in the bones[110] Clinical studies have shown that in rickets there is an increased excretion of both calcium and phosphorus in the feces, but the balances have not always been found negative even in severe cases[111]

tain extent by the diet Diets high in calcium and low in phosphorus when the Ca P ratio is 4 1 or higher are rachitogenic as are diets low in calcium and high in phosphorus if vitamin D is lacking Certain cereals such as corn and oats have a rachitogenic effect due to the fact that their phosphorus occurs as phytin (inositolhexaphosphoric acid) which is a relatively insoluble form In practice, however rickets can be prevented or cured in infants by the giving of vitamin D despite a rachitogenic diet and is not accomplished by the addition of calcium or phosphorus to the diet

Local Effect of Phosphatase The enzyme phosphatase has the property of splitting organic phosphorus compounds into inorganic phosphate It is believed that if phosphorus esters were present in bone tissue the enzyme phosphatase would tend to change these into inorganic phosphate an important step in the precipitation of calcium phosphate Such a change in the bones has never been proven, although the phosphatase content of cartilage is the highest in the body It would seem therefore, that the increase in phosphatase in rickets is in a sense a protective mechanism which tends to maintain an adequate concentration of calcium phosphorus and carbonate ions so that normal precipitation in bone may result Just what happens in the vitamin D deficiency state which permits a lowering of the inorganic phosphorus in the blood below 3 0 mgm per 100 cc when the serum calcium is normal is unknown There is certainly no disturbance of the calcium phosphorus ratio in the rachitic bone A proportionate reduction occurs with relative increase in organic matter and water with an otherwise normal diet According to Shohl[112] it is primarily the utilization of calcium and phosphorus which determines the rate of growth of bone and it is the interrelations of calcium and phosphorus and vitamin D which determines the development or the cure of rickets

Symptomatology

The onset of the disease is insidious and the exact date often is impossible to determine The symptoms may be grouped under four main divisions (a) constitutional, (b) osseous (c) visceral (d) nervous

Constitutional Symptoms The child usually is irritable and restless This is evidenced by the disturbed sleep and by the baldness of the scalp over the occipital region from the constant rolling of the head upon the pillow into which it seems to burrow Lateral decubitus often is preferred by the child There is usually such profuse sweating of the

histological changes plus the mechanical strains resulting from movement and weight bearing

Pulmonary lesions are invariably present, due in part to the deformity of the thorax Thus, there is atelectasis of the lung beneath Harrison's groove with emphysema of the portion anterior to it Bronchitis, both acute and chronic, and bronchopneumonia are frequent findings post mortem The gastrointestinal tract reveals a low grade chronic catarrh often associated with dilatation of the stomach and intestines The spleen commonly is enlarged because of a simple hyperplasia Amyloid changes have not been reported consistently The liver is enlarged less often The lymphatic glands are found enlarged in a considerable percentage of cases and are associated invariably with the splenic tumor They, too, show merely a simple hyperplasia The muscles are flabby from imperfect nutrition and sometimes atrophy from disuse but present no characteristic anatomical change Microscopically they may reveal a blurring of their striations and sometimes fatty infiltration

Pathological Chemistry

The chemical changes which may be detected in the blood in rickets are as follows

(a) Phosphatase Normal blood serum values are from 5 to 15 Bodansky units per 100 cc In mild cases of rickets values of 20 to 30 units are common, in severe rickets 60 units or more may be found This change is the first to come and the last to go as a rule It may antedate radiological changes in the bones and is thus a valuable early sign of rickets unless its elevation can be explained on some other basis It is not reduced however in the rachitic cartilage

(b) Serum Phosphorus In healthy infants the inorganic serum phosphorus amounts to from 4 5 to 6 5 mgm per 100 cc whereas in rickets values of 1 5 to 3 5 mgm per 100 cc are commonly encountered This low serum phosphorus level is thought to be due to two factors faulty absorption from the intestinal tract, and to a lesser extent, failure of normal reabsorption of phosphates by the renal tubules after filtration through the glomeruli

(c) Serum Calcium The serum calcium usually is normal in rickets though under certain conditions it may be reduced to a point where tetany develops Factors which influence calcium level are, as in the case of phosphorus, factors of absorption and retention These are controlled in part at least by vitamin D Absorption is influenced to a cer

its nature depending largely upon the stresses and strains to which the bone is subjected The underlying pathological changes are present constantly, even though no deformity is evident

The *skull* often is strikingly large in contrast to the face especially in older children The upper jaw is decreased transversely but increased sagittally so that it is projected forward, while the converse is true of the lower jaw The incisor teeth are often bent sharply inward so that, when the mouth is closed a space of several millimeters exists between the lingual surface of the upper and the labial surface of the lower teeth The cranium usually has a square appearance from a thickening of the frontal and parietal tuberosities and flattening of the occiput This is indicated by the caput quadratum or hot cross bun head If the parietal bones are especially prominent, the name of caput natiforme is given Quant[72] has described also a type of skull deformity in 60 per cent of his cases, which he has called tribounocephaly or three hilled skull in which owing to transverse and certical depressions in the occipital bone the skull appears to bulge to an abnormal degree on each side as well as above The anterior fontanelle which usually closes by the 15th or 16th month often remains patent in rickets to the 3rd year or even later The posterior and two lateral fontanelles, as well as the coronal lambdoid and longitudinal sutures may remain open also Further the edges of the fontanelles and particularly the bone in the region of the lambdoid suture are softened and easily compressible This softening known as craniotabes occurs in round or oval patches a quarter to one inch in diameter situated near but not actually reaching the suture Pressure over these patches yields a peculiar creaking sensation not unlike parchment under the pressure of the finger Fraser[3] reports that some 29 per cent of skulls of rickety children under 3 years of age showed some degree of craniotabes That craniotabes is not always of pure rickety origin is admitted by Barlow and Lees[7] who found in 100 cases of craniotabes 47 per cent with a definite syphilitic history or stigmata of the disease

Dentition always is delayed to a greater or lesser extent The first tooth may not appear until the 15th or 16th month but when once the eruption begins it goes very rapidly Whether rickets plays a part in the production of dental caries is disputed Inasmuch as calcification of the temporary teeth is well advanced at birth it seems unlikely that the disease could exert any great influence upon their formation The permanent teeth which undergo calcification during the first year in-

scalp that the pillow case will be found wet through Hess claims that this head sweating is characteristic of the disease, but Still attaches very little diagnostic significance to it Sudamina over the trunk and extremities may also result Marked vasomotor instability and eczema are not uncommon The eyes are rounder than normal and show more of the sclerae than those of the healthy child, according to Jauristi [1] The temporal veins often are dilated in severe cases with marked cranial involvement There is rarely, if ever, fever in an uncomplicated case, indeed a subnormal temperature is the rule There is more or less pallor of the skin and flabbiness of the muscles, while the subcutaneous tissues and body weight may be well retained

A lack of proper muscular tone is present in most cases and in many to a marked degree, thus the child may not be able to walk, to stand or even to sit up It is seen also in the extraordinary abnormal positions in which the limbs may be placed Hagenbach-Burckhardt[39] considers it a specific weakness of the muscles, but Stoeltzner[5] believes it is an interception of the innervation,' in other words, an inhibition of nerve stimuli because of the pain produced by the muscular contractures in the softened, thickened periosteum The weakness of the lower extremities may be so marked as to suggest a true paralysis, and in fact it may be necessary to demonstrate the normal electrical reactions of muscle and nerve to exclude a poliomyelitis The malnutrition of the muscles is manifested also by the tendency to potbelly and constipation both of which are frequent symptoms of rickets The abdomen is uniformly enlarged everywhere tympanitic often to a marked degree This tympanites is due to a lack of tone, both in the abdominal muscles and in the muscular coats of the stomach and intestines, in the same way the constipation is an atonic one There may be a chronic catarrh of the stomach and colon resulting in dyspepsia and anorexia, vomiting the discharge of much mucus, or alternating attacks of constipation and diarrhea The lack of tone in the costal muscles may result in a predominance of the diaphragmatic type of respiration There is also a tendency to respiratory cararrhal inflammation such as laryngitis and bronchitis All these general features may be present for two or three weeks before the osseous changes are manifest or again they may be so slight as to be entirely overlooked

Osseous Symptoms The two main features ars softening and deformity The softening affects principally the flat bones and the diaphysis of the long bones but the deformity may affect any bony part

sitting position The fingers may present a bead like appearance from their thickened and spindle shaped condition

The *pelvis* reveals a thickening of the iliac crests in some cases narrowing of the pubic arch lumbar lordosis flattening and broadening of the ischial tuberosities, with a horizontal coccyx The pelvic cavity is smaller than normal due in part to the occasional inward direction of the sacral convexity The femora present an enlargement of the distal epiphyses and an anterior bowing of the diaphyses The lower leg shows an enlargement of the upper epiphyses but to a lesser degree than the distal Incomplete fractures are common An outward rotation of the entire leg occurs genu varum and less commonly genu valgum, may be seen and in this way bow legs O legs and knock knee X legs develop Still found slight or marked curvature of the tibia and fibula in 43 per cent of his cases The commonest deformity is a bending outward of the lower third of the tibia which is combined sometimes with a forward bowing either slightly convex or angular, of the lower third In severe cases there may be a diminution of the growth of the skeleton which together with the bowing of the femora and tibiae results in more or less dwarfism Further the gait usually is waddling because of the deformity of the pelvis and the lower extremities It should be borne in mind that these various osseous changes appear in definite chronological order Thus the craniotabes and the rosary occur usually in the first six months The thoracic changes are most marked during the second six months while the deformities of the legs occur chiefly in the third six months when the child is more apt to be running about

Visceral Symptoms Owing to the slanting forward of the child s pubes and abdominal wall to the relaxation of the suspensory relation of the penis and to the hypotonicity of its vascular elements the penis hangs low straight and long (Jauristi) The liver commonly is displaced downwards by the thoracic deformity and in severe cases, complicated by anemia may be actually enlarged The spleen also may be enlarged, when there is a marked anemia Cheadle [5] has suggested that the hepatic and splenic hyperplasia depend either upon a mechanical hyperemia due to an obstructed pulmonary circulation and feeble cardiac muscle or to an irritative stimulus of unknown nature, of course an associated congenital syphilis may account for some cases

The lymph nodes of the neck may be definitely enlarged, when there is much nasopharyngitis with chronic tonsillitis and infection of the adenoid tissue in the posterior fauces This adenopathy may be more

variably suffer. Still[1] suggests that the changes in the temporary teeth may be due to the unhealthy condition of the saliva incident to improper and indigestible food. Be this as it may, both temporary and permanent teeth show horizontal and longitudinal depressions with more or less discoloration. The cutting edge presents sharp points. Of the permanent teeth, the central and lateral incisors, the tips of the canines, and the crown of the first molars are affected most. It is of interest to note that Mallanby[47] has reproduced successfully in young puppies on a deficient diet a delay in the loss of the deciduous teeth, delayed eruption of the permanent teeth, irregularity in position and overlapping of the incisors, partial absence of the enamel, and a low calcium content of the tooth.

The *spine* frequently reveals a kyphosis of the lower dorsal and lumbar vertebrae, less commonly a scoliosis. Kyphosis existed in 46 per cent of Holt's series [illegible]

The *thorax* reveals almost constantly the so called rachitic rosary, due to an enlargement of the costochondral articulations, particularly pronounced in the lower ribs. This, though visible in emaciated children, frequently is elicited only by palpation. In severe cases there may be also flattening of the lateral portion of the chest wall, especially between the midclavicular and postaxillary lines and between the fourth and seventh ribs resulting in the chicken- or pigeon breasted appearance, pectus carinatum. Whilst the central portion of the chest is flattened, the lowest region may project outwards forming the Harrison groove, which no doubt is exaggerated by the inward pull of the diaphragm. The lower portion of the thorax may bulge to a striking degree because of the enlargement of the liver. There are two main factors at work in the production of the thoracic stigmata, atmospheric pressure and the softness of the chest wall, which sucks in at the points of least resistance, namely, the costochondral articulations, obstruction to the entrance of air by bronchitis, enlarged tonsils, or adenoids increases the deformity.

The *clavicle* may suffer from an exaggeration of its normal curves or *even from fractures. The humerus rarely is deformed* except in severe cases, though the distal epiphyses may be enlarged and the diaphysis shortened to a marked degree. The enlargement of the epiphysis at the wrist is the most constant symptom of rickets. The shafts of the radius and ulna show usually a convex curvature as a result of the forces exerted upon the bones when the child attempts to support itself in the

tion and flexion of the hands to the ulnar side with extension of the fingers into the main d accoucheur' attitude The feet may be extended and the toes flexed Spasms may occur elsewhere, as in the muscles of the larynx giving rise to a crowing sound during inspiration Laryngismus stridulus was present in 89 per cent of 443 cases collected by Kirchgaesser[8] This contracture may be of such a degree as to cause partial suffocation

When these symptoms are not present they may be elicited in the following manner (a) tapping over the facial nerve just below the posterior part of the zygoma will produce a sudden contracture of the facial muscles on the same side, Chvostek s sign (b) constriction of the upper arm so as to obliterate the pulse will often cause a typical carpal spasm Trousseau s sign, (c) with a galvanic current the cathodal opening contraction occurs with very low currents five milliamperes or less Erb s sign Anodal hyperexcitability is not of the same diagnostic significance though present

The significance of the enlargement of the head which so often occurs is uncertain Hess believes that it is associated usually with a mild grade of hydrocephalus Nystagmus strabismus and spasmus nutans occasionally occur Thomson[83] found rickets in 33 out of 35 cases of head nodding

Umbilical hernia and diastasis recti abdominalis are common sequelae of the atony of the abdominal wall and the tympanites Gastrectasis is frequent if not constant according to Comby it may survive the osseous deformities and result in long continued dyspepsias Further colitis especially in summertime is often very severe or even fatal One of the most common and alarming complications of the disease is a capillary bronchitis or actual bronchopneumonia to which there is an especial predisposition owing to the chest deformities Indeed even the most trivial respiratory infection should be treated with the utmost care for this reason The liability to tuberculosis not only in the lungs but elsewhere is said to be increased in rickety children

Time of Onset, Duration, and Course

The first symptoms of rickets appear after the third month most commonly between the sixth and twelfth months but sometimes may develop during the 1st month especially in premature infants Only exceptionally do the first symptoms develop after the end of the second year Those which occur after the second year usually are of the

generalized and found to a slight degree in most of the superficial lymph nodes The blood in the majority of moderately advanced cases is below par There is usually a simple secondary anemia with a diminution chiefly of the hemoglobin and only slightly of the red cells According to Morse [6] and others, this anemia may or may not be accompanied by a leucocytosis A leucocytosis occurs more frequently in the cases with splenic tumor than in those without This leucocytosis may be due to an increase of any one or of all varieties of the white cells In some cases therefore, the embryonic and immature type of cell is common as is true of all severe anemias, whatever the cause

The urine often is diminished in quantity and may have an unusually offensive odor, while the acidity is diminished Whatever be the importance of the calcium metabolism in the pathogenesis of rickets one must note that Baginsky,[44] Schabad,[68] Orgler, and Dibbelt [8] have found in the florid stage of rickets that the calcium output is increased enormously in the stools but decreased in the urine, while in the stage of convalescence there is a marked diminution in the feces with a slight increase in the urine Chronheim and Muller,[79] Meyer,[80] and others have found so little change in the calcium balance as to warrant no definite conclusions Schloss[81] in one of his series of papers on the metabolism of rickets notes that in the progressive stage of the disease phosphorus is excreted in the feces much more than in the normal condition, and that following cod liver oil medication as improvement progresses, the phosphorus loss by the intestine is reduced materially

Nervous Symptoms The close association of rickets and tetany has long been recognized, and tetany usually is regarded as part of the rickets symptomatology In Still's series of 24 cases of tetany 22 showed definite and one doubtful rickets The age incidence is the same, the peak of the cases of tetany occurs in early spring, and no cases are seen in summer However, common as is rickets in tetany, the reverse is not true and the great majority of the cases of rickets do not show tetany [114] Furthermore, rickets show a diminution in the concentration of phosphates in the blood serum, whereas these substances are either normal or increased in idiopathic tetany It would seem, therefore that tetany in rickets is likely to occur only when the serum calcium is materially reduced which is not often It might be argued with reason that when lowering of the blood calcium does occur in rickets, it is due not to that disease but to the simultaneous presence of idiopathic tetany The tendency to tetany, when present, gives rise to carpopedal spasms, rota

nonrachitic families they are often as late as the ninth or even the eleventh month

For an early diagnosis the occurrence of the rachitic rosary is far more important than the pliability of the thorax It must however be borne in mind that physiologically there are slight swellings of the costal ends of the cartilages just as of the epiphyses of the long bones Hess and Unger[94] believe that 'there is not only rachitic but also ascorbutic beading' both in the human and experimental scurvy, and they believe this factor is largely accountable for the confusion that existed between infantile scurvy and rickets

Where biochemical analyses are possible the lowering of the blood phosphorus may be used as corroborative evidence as it usually shows a decided drop even before demonstrable bony changes On the other hand the lowering of the blood calcium is a later change and may or may not be present Where tetany is a feature the blood calcium invariably is low

The variability of the presenting symptoms in rickets and the consequent difficulty in diagnosis is emphasized by Still who points out that the child may be brought to the physician for convulsions for enlargement of the abdomen for bronchitis for profound anemia or for muscular weakness In all these the bone manifestations may be limited to slight beading of the ribs lateness in dentition and delay in the closure of the fontanelle yet the disease is none the less rickets

Roentgen Diagnosis

Prior to 1910 Reyher, Schmorl and even Fraenkel stated that there were no constant or typical changes in the skiagram Later however Fraenkel and Lorey[95] Wohlauer[96] Lovett,[97] Jacobsohn,[98] Albert-Weil[99] and Baetjer[100] emphasized the value of X rays especially for determining the stage of the disease and for recording the progress of healing

The main points in the skiagram of rickets are (1) the delayed ossification and indistinctness of the epiphysis (2) a fraying out of the end of the shaft next to the epiphysis presenting a beaker like or saucer shaped outline (4) cortical thickening on the concave side of the curved bones (5) areas of diminished density in the bone shadow of the shaft due to the lack of calcium (6) periosteal thickening and multiple fractures in advanced cases (7) an absence of periosteal hemorrhage In the stage of healing there is seen a reaccumulation of the calcium in the form of a narrow irregular band which becomes broader denser and

coeliac or renal type An undoubted case of congenital rickets has not been reported so far, though rachitic-like changes have been described in fetal bones Many of the supposed cases of *congenital rickets* are to be considered rather as examples of osteogenesis imperfecta, a disease which has nothing in common with true rickets from the pathological standpoint On the other hand, Barlow, Cheadle, and others admit the possibility of the occurrence of the disease in utero, especially if the maternal health be impaired

The term, *rachitis tarda* or *recrudescent rickets,* indicates the occasional occurrence of the disease after years of quiescence, sometimes as late as the fifteenth year This occasionally may be the primary attack However, apart from the curvature of the bones, such cases usually have no other evidence of rickets and should be considered as osteomalacia rather than true rickets Nevertheless, beading of the ribs, enlargement of the epiphyses, coxa vara, scoliosis, genu valgum and very occasionally, enlargement of the head have been described in children between nine and 14 years of age by Ransford,[86] Barlow,[7] Palm,[60] Duplay,[87] Cautley,[88] Kirmisson,[89] Clutton,[90] Ricklin,[91] Radice,[92] and Looser[93] Looser believes that rachitis tarda is more common than is generally supposed, and that it forms the link between the rickets of infancy and osteomalacia This belief receives apparent support in a paper by Bohme[94] who states that the same external conditions sometimes produce rickets and sometimes osteomalacia, and that from the pathological standpoint the two diseases cannot be differentiated

The course of rickets is essentially a chronic one and runs from 3 to 15 months There is no really acute form as far as is known, since the cases of so-called acute hemorrhagic rickets are recognized at the present time as being cases of infantile scurvy

Diagnosis

The history of imperfect feeding together with evidence of enlargement of the skull beading of the ribs thickening of the epiphyses lack of muscle tone and delayed dentition suffice in the maority of cases to make a positive diagnosis of rickets Craniotabes of nonrachitic origin may occur in the new born but in this type the depressible area usually is not limited to the occipital bones, and it reaches its full development in the first week or at the latest the first month after birth Further, without other evidence of rickets, a diagnosis of rickets cannot be made from the age of eruption of the first teeth, for in some

but the presence of other rachitic stigmata, to say nothing of the skia gram, should suffice to clear up the diagnosis

Prognosis

Holt writes categorically that rickets per se is never a fatal disease though it is a large factor in the mortality of the first two years as the cachexia it produces predisposes strongly to every form of acute disease The outlook is good if the patient be placed under suitable treatment the tendency certainly is towards recovery The real danger to life lies in the pulmonary complications bronchitis and bronchopneumonia but death may result also from convulsions or even laryngismus stridulus According to Engel[101] as a result of food deficiency during the war rickets and its respiratory complications caused in 1918 a mortality among children from two to five years of age greater than the infant mortality

The majority of the severe deformities disappear gradually during childhood rarely, however in severe cases some deformity persists through life, rachitic dwarfism may result or malformation of the thorax and spine may persist and in turn lead to cardiac insufficiency and to pulmonary disease The malformations of the pelvis are common causes of obstetrical complications

Prophylaxis

Both the Toverruds[116] and Mallanby[47] consider a poor diet of the mothers during pregnancy as one of the chief predisposing factors in the development of rickets in infancy Therefore the first step in the prevention of rickets in the child should be an adequate intake of calcium and vitamin D by the mother during the last trimester of pregnancy A calcium intake of at least 1 4 to 1 6 gm of calcium daily is necessary for retention of the amount of calcium needed by the fetus If the calcium content of the diet is below these values even the addition of vitamin D may not insure retention Although the optimal amount of vitamin D during the later months of pregnancy has not been determined with certainty 800 units per day together with a diet rich in calcium and phosphorus is recommended What is true of pregnancy is even more true of the period of lactation when the drain on the mother may be even greater[117,118] The prevention of the disease in normal artificially fed babies requires between 400 to 800 international units of

more regular as the stage of complete cure is reached Lastly, the skia gram of the chest will show marked pulmonary changes due to pressure atelectasis along the anterior margin of the lungs

Differential Diagnosis

Infantile myxedema, infantile scurvy, and congenital syphilis occa sionally may be suggested *Infantile myxedema* may also present swell ing of the costal cartilages and of the epiphyses of the long bones, de layed dentition, patency of the anterior fontanelle, and slowness in learning to walk However, the cretinoid facies, the retardation of the mental development, the macroglossia the myxedematous deposits in the subcutaneous tissues, the dry harsh skin, the scanty brittle hair present a picture that is difficult to confuse with rickets

Infantile scurvy may coexist with rickets, and the two diseases still are mistaken often for one another In scurvy the tenderness of the legs is marked, while it is not present in rickets In the former disease the osseous swellings are found in the diaphysis proper, though often near the epiphysis, and are due to the subperiosteal hemorrhages Lastly the gingivitis and the cutaneous and orbital hemorrhages of scurvy should serve to distinguish the two diseases

Congenital syphilis may offer considerable difficulty In Parrot's[19] syphilitic pseudoparalysis there is either a thick ridge which surrounds the bone just at the epiphyseal margin, or a spindle-like swelling which involves both the epiphysis and the end of the diaphysis Further, there is a complete flaccid pseudoparalysis, often unilateral or at least more pronounced on one side and affecting only one or two joints, most com monly the lower epiphysis of the humerus Lastly, it is a disease chiefly of the first three months a time at which rickets rarely occurs

Hydrocephalus is suggested sometimes in marked cranial rickets, but in the former disease the entire skull is affected symmetrically, especially the lateral areas lying below the frontal and parietal tuberosities *The congenital funnel breast* is differentiated from rickets by the tremendous retraction of the inferior end of the sternum In the true pigeon breast the projection is acutely angular and results from pertussis, repeated attacks of bronchitis, or postnasal adenoid growths and may occur in dependently of any rachitic softening *Pott's disease* should be differen tiated easily by the sharp localization of the kyphosis, while the rachitic spine presents a gentle curve rather than an acute angle *Congenital dislocation of the hip* may be suggested by the coxa vara of rickets

unusually susceptible to sunlight, it should be protected by applying a thin coating of oil or vaseline before exposure The eyes usually are protected although Hess believes this precaution unnecessary

Artificial Sources of Ultra-Violet Light In using artificial sources of ultra violet light for the cure of rickets it must be remembered that the intensity of these rays is much greater than of sunlight They may be as high as 20 per cent of the total energy as compared with 0 15 per cent for sunlight in midsummer Greater care must therefore, be exercised particularly during the initial exposure The air cooled, mercury-vapor lamp is a much more powerful source than the carbon arc In general the dosage should induce a slight erythema For the mercury vapor lamp the child should be placed at a distance of three feet from the source and the initial treatment limited to two minutes front and back Treatments should be continued every other day for four weeks the time of exposure being increased by one minute each session

The effects of heliotherapy whether natural or artificial are striking Within 10 to 14 days radiographs will show new calcification at the epiphyses as well as calcification of the carpal centers The blood phosphatase drops the inorganic phosphorus rises and there is rapid improvement in the nutrition of the skin and the muscles In this connection it should be remembered that neither sun s rays nor ultra-violet light from artificial sources will confer a permanent cure Luce Clausen[214] frequently has observed a second attack of rickets develop in spite of a thorough course of irradiation during the previous winter

Cod Liver Oil Cod liver oil is the time honored remedy for rickets It has many advantages It has no toxic effects it is extremely effective and it is universally available On the other hand it is somewhat slower in its action than the pure vitamin and sometimes it is not sufficiently potent in dosages tolerated by the average infant to cure rickets in some premature babies and in especially susceptible full term infants and older children Park[119] states that it is impractical to give more than four full teaspoons of cod liver oil per day to an infant Cod liver oil of standard strength contains not less than 85 units per gram Most oils run as high as 100 units per gram Four full teaspoons about 4 gm would supply about 400 units per day an amount adequate for ordinary purposes but insufficient in certain refractory cases In such cases the cod liver oil must be fortified by additional activated 7 dehydrocholesterol or halibut liver oil which is many times more effective must be substituted in its place

vitamin D daily according to the Food and Nutrition Board of the National Research Council Normal babies breastfed require somewhat less, but just how much less is not known definitely Prematurely born infants require at least double this amount For children between infancy and adolescence a quart of milk and 300 to 400 units of vitamin D daily permit ample retention of calcium and phosphorus

Treatment

The treatment of rickets whether in the premature infant during his first months of extra-uterine life or in the full-term infant who develops the disease in later months is essentially the same It consists in the adequate administration of vitamin D from one or all sources available

Correction of Rickets The correction of rickets, once developed, depends upon the ingestion of vitamin D in optimum amounts and a diet containing abundant calcium and phosphorus So far as vitamin D treatment is concerned, the chief sources of the vitamin are three fold, irradiation of the rachitic child, the giving of cod liver oil, percomorph oil, and/or one of the products of irradiated ergosterol These will be considered separately, although it is customary, even advisable, to combine these in the treatment of rickets

Ultra violet light—Sunlight? The observations of Hess[63] have demonstrated that quality and intensity of the protective radiations are of more importance than their duration He showed that New York has the same number of hours of sunlight during February and March as London has during summer months, yet rickets is prevalent in New York during spring months, whereas the disease undergoes healing in London during the summer He believes that the difference cannot be explained on the basis of time spent out of doors but is rather the result of the quality of the protective rays Smoke and dust cause marked decrease in the curative effect of the sun The passage of sun's rays through a deep layer of atmosphere, as when the sun's altitude is small, interferes greatly with the penetration of the effective rays which occur in a narrow band ranging from 296 to 310 millimicrons (2,960 to 3,100 angstroms) According to Hess the first exposure to sunlight should be over the legs and of not more than 10 minutes duration The susceptibility of the child to ultra-violet light thus is determined Thereafter the time is increased by five-minute intervals and the treatment extended to the arms and trunk as weather permits If the patient's skin proves

fear of any deleterious influence As a rule the dose of vitamin D which prevents rickets, will cure it effectively but more slowly than is desirable Park[119] suggests that premature infants should be given a daily dose of from 10 000 to 20 000 units or occasionally more in refractory cases and older children as much as 60 000 units daily After a month s time when the rickets has been controlled effectively the dose may be reduced gradually to 1 000 to 2 000 units per day In some children who show a persistent tendency to rickets the larger dosage must be maintained indefinitely

Diet The diet in rickets should be rich in calcium and particularly phosphorus The deleterious effect of high carbohydrate diets in rachitic children has long been recognized Mellanby demonstrated the decalcifying effect of diets rich in wheat germ and oatmeal and to a lesser extent white flour rice and other cereals Experimentally this effect can be partially abolished by boiling the cereal in 1 per cent hydrochloric acid He concluded that the cereals contained a toxic factor which was destroyed by the boiling acid but recent experiments by Bruce and Callow[1 9] indicate a more plausible explanation These investigators found that the phosphorus in cereals such as oatmeal is in an unavailable form inositolhexaphosphoric acid which is hydrolized into available phosphorus by boiling in acid

Orthopedic Treatment

Orthopedic treatment of deformities had best be delayed until the fifth or sixth year though angular deformities of long bones and fractures must be attended to in the active stage of the disease Gymnastics may help to overcome thoracic deformities and should be commenced at an early stage of the deformity

Endogenous Rickets

When ordinary vitamin D therapy *fails* the question of endogenous rickets should be raised It is now customary to divide these cases of rickets into four groups which are probably different in etiology

(a) Vitamin D Refractory Rickets It is customary to place in this group all children of 18 months or older who have X ray evidence of rickets despite customary prophylactic dosage of vitamin D and in whom the serum content of vitamin D is normal The reason for failure is seldom apparent since the clinical X ray serological and metabolic manifestations are those encountered in ordinary cases It is believed

Percomorph Oil Among the wide variety of substitutes for cod liver oil is percomorph oil This oil is obtained from such fishes as the tuna, the swordfish, the red snapper, and certain species of sea bass When refined it contains not less than 180 international units per drop so that two to three drops per day are adequate protection against or even cure of rickets when the formula is made from vitamin D milk or from four to five drops per day when unmodified milk is used

Artificial Preparations of Vitamin D (1) *Viosterol* in oil is ergosterol activated by irradiations and dissolved in some bland oil such as corn oil If of standard potency, one gram of the oily preparation contains approximately 10,000 units One drop from a standard dropper contains [illegible]2 units, or more than is present in two full teaspoons of cod liver oil The preparation is odorless and tasteless It is best administered by dropping it directly into the mouth of the child rather than by addition to the feeding

(2) *Calciferol in propylene glycol* This preparation, said to be pure vitamin D, has the advantage over other preparations with an oily vehicle in that it is water soluble and can be dissolved in orange juice or any watery feeding

(3) *Irradiated cholesterol* This form of vitamin D is activated 7 dehydro cholesterol prepared by irradiating cholesterol Its potency compares favorably with other similar preparations according to Drake Tisdale, and Brown[1 1]

(4) *Cod liver oil concentrates* These preparations are concentrates from fish liver oils combined with carotene They are prescribed in liquid, capsule, or tablet form

(5) *Vitamin D milk* Irradiated vitamin D milk is produced through exposure of a thin film of the milk to ultra-violet light Standard preparations contain at least 135 units per quart It has the advantage that the vitamin comes with the bottled milk or is obtained in evaporated or dried form Its low vitamin D potency can not be raised because of the unpleasant taste imparted to the milk Metabolized vitamin D milk is produced by feeding the cow irradiated yeast a potent source of ergosterol Its potency in rat units is approximately three times that of ordinary irradiated milk[1 1-3]

As regards dosage of artificial preparation of vitamin D most authorities agree that from 800 to 1 000 units per day should be regarded as the lowest level which it is wise to employ for the infant In refractory cases much larger doses 10 000 to 30 000 units, may be given without

is lacking Indeed it has been suggested that the term renal rickets be abandoned and replaced by renal osteitis fibrosa—generalizata or cystica Another factor causing calcium deprivation according to Mitchell[131] is the shift of phosphate excretion from the kidney to the intestine In the latter the phosphate combines with calcium in the food to form insoluble calcium phosphate thus blocking calcium absorption The prognosis is necessarily grave due to the underlying renal insufficiency

(d) Celiac Rickets In celiac disease rickets with or without hypophosphatemia is sometimes encountered The bony changes are characteristic of rickets *Fat is not utilized fatty acids are excreted in the* intestine where they form calcium soaps thus interfering with calcium absorption As a consequence *fatty diarrhea* a negative calcium balance, low serum calcium tetany and decalcification with resultant skeletal deformities and dwarfing occur Vitamin D apparently is not absorbed and this may be of fundamental importance since recovery promptly follows the exhibition of the vitamin through ultra violet irradiation or one of the non fatty vitamin D components

(e) Lignac-Fanconi Disease[133] Cystinosis or Cystine Diathesis may be the calse of vitamin D resistant rickets in childhood or infancy It is a familial disease inherited as a recessive trait and due to a disturbance of catabolism of cystine and its precursors homocystine and methionine The results are deposition of cystine crystals in the reticuloendothelial system damage to the kidneys and inhibition of growth The disorder is characterized by anorexia excessive thirst and evidence of renal disease In infants hypophosphatemia is usual but the reverse is true in the older age group The type of rickets occurring in this disease is also resistant to vitamin D therapy

Rickets Occurring Beyond Infancy

It has been suggested by Warkang[13] that the terms juvenile adult and senile rickets should replace the terms late rickets osteomalacia and hunger or war osteopathy since the process is basically the same in different age groups These cases also have in common a good response to vitamin D therapy

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that the condition is due to an unexplained hypophosphatemia Albright Butler, and Bloomberg[14] reported the case of a boy of sixteen with rickets persisting from infancy requiring over a million units per day to induce healing P V Wooley, Jr,[130] whose case required a daily dose of 150,000 units of viosterol and 25,000 units of percomorph oil before signs of healing occurred, cautions against the indiscriminate administration of colossal doses of vitamin D He feels that renal damage is not likely to occur so long as the serum calcium remains normal and excretion in the urine is not increased If the urine shows a positive reaction with Sulkowitch s reagent, then the dosage of vitamin D should be materially reduced

(b) Fanconi (de Toni-Debre) Syndrome[18] Cases falling into this group commonly exhibit a hereditary background Stunting of growth is usual Hypophosphatemia is present The urine may contain glucose and albumen without azotemia or hyperglycemia Pathological changes observed include fatty vascular degeneration of the tubular epithelium of the kidney and cirrhosis of the liver Vitamin D therapy is not effective

(c) Renal Rickets In renal infantilism the etiology of rickets is of great interest, both academically and clinically, because it has a different cause and demands a reversal of treatment The primary cause is not vitamin D deficiency, according to Parsons, but an inability of the kidney to excrete phosphorus properly According to the formula of Freudenberg and Gyorgy,[8] the concentration of ionized calcium in the blood together with the bicarbonate and phosphate ions is a constant for any given hydrogen ion concentration In renal infantilism the increase in ionized calcium in the blood or in cases, where the calcium is normal, by a reduction in bicarbonate ions In the latter case the phosphorus ion increase is balanced by acidosis In the former the stores of calcium are depleted gradually as nature attempts to elevate the level of free or ionized calcium of the blood The bones thus are decalcified gradually in nature's effort to elevate the level of the ionized calcium in the blood Thus, it is clear that vitamin D therapy is contraindicated because it tends to increase the blood phosphorus Parsons[84] has supported this theoretical observation by demonstrating clinically that renal rickets progresses during vitamin D feeding and shows healing when it is stopped Although the bony changes, which accompany chronic renal insufficiency in childhood resemble rickets radiologically, there are histological differences Under the microscope the lesions resemble more those of osteitis fibrosa cystica, since osteoid formation

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CHAPTER XI

SCURVY

BY EDWARD S. MILLS

TABLE OF CONTENTS

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CHAPTER XI

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TABLE OF CONTENTS

Introduction

Synonyms Scorbutus, infantile scurvy, Barlow's disease, Moeller Barlow's disease

Definition Scurvy is a disease caused by a deficiency of vitamin C and is characterized by great debility, anemia, mental apathy, a spongy condition of the gums, and a tendency to hemorrhages into the sub cutaneous tissues and from the mucous surfaces

Historical The disease unquestionably was recognized by the Greek and Roman physicians, as Pliny gives a good description of it in his Natural History in the first century Joinville in 1260 gave the first account of the disease among the troops of Louis IX during his campaign in Egypt The earliest description of maritime scurvy was written in 1497 by Vasco da Gama, who had lost 100 of 160 men by the time his expedition had reached the Cape of Good Hope

The present name, scorbutus, first appears in medical literature about the beginning of the sixteenth century Lind,[1] in 1752, published the first monograph on the subject and one that has proved to be the classic of the disease In 1795, upon the recommendation of Sir Gilbert Blane lime juice was added to the daily ration of the British navy and later to the mercantile marine The bibliography became enormous in the eighteenth and nineteenth centuries as illustrated by the collection of 773 papers by Krebel (quoted by Immermann) up to the year 1861

The foundation for our present conception of scurvy was laid by the experimental work of the Danish scientists Axel Holst and Theodore Frolich[3] in 1907 and by the chemical researches of Casimir Funk,[4] who in 1913 originated the vitamin theory of the pathogenesis of the disease A F Hess[5] of New York, in his book on the disease, gives a good review of the pathology The monographs of Aschoff and Koch[6] and of Hojer,[7] the former based on human postmortem material and the latter on the experimental disease in guinea pigs, are among the most valuable recent contributions to the pathogenesis and treatment of the disease

The studies of Crandon Lund and Dill[10] [106] on the effects on man of a long-continued diet lacking vitamin C have added knowledge of great importance

The infantile form of scurvy was described first by Moeller[8] of Koenigsburg in 1859 under the misnomer of acute rickets The first suggestion of the true nature of the disease was by Ingerslev,[9] a Swedish physician in 1873, but it was Cheadle[10] of London who, in 1878, first

clearly emphasized the identity of the infantile and adult cases Five years later (1883) Thomas Barlow[11] by his pathological and clinical studies established once and for all the identity of the two diseases In view therefore, of the universal acceptance of the identity of infantile and adult scurvy, we will consider them together, merely emphasizing the clinical features of each type

Etiology

Incidence Epidemics have occurred on land in times of war and famine and under normal conditions in badly provisioned and overcrowded public institutions When the potato crop failed in Ireland in 1846 scurvy became very prevalent Hirsch[12] has collected records of 110 epidemics 11 of which occurred in Great Britain In Aruba a small island of Dutch Guiana lying north of Venezuela there appeared in 1915 following three years of crop failure 3 000 cases among a population of 10,000 (Tobler[13]) In the Crimean War (1854 6) 23 000 cases occurred among the French troops alone[14] In the American Civil War (1861 5) there were in all 30 174 cases of scurvy with 383 deaths during the five years covered by the statistical report[15] In other words 15 per cent of the deaths were assigned to scurvy Paris and Metz suffered severely during the Franco Prussian War of 1871 In the concentration camps in South Africa during the Boer War (1899-1900) scurvy was not uncommon At the fall of Port Arthur during the Russo Japanese War there were according to Sato and Nambu[16] 17,000 sick and wounded Russians of whom more than 50 per cent had scurvy Blau[17] reports an incidence of 4 628 cases in the Russian army during 1906 In spite of the wonderful advances in the transport and commissariat services evidenced during World War 1 scurvy was not unknown among the various armies including the French (Carvier and Benoit[18]), Italian (Vanutelli[19] and Vallardi[20]) British (Dyke[21]) Mesopotamia Commission and Serbian (Wiltshire[23])

Scurvy has been responsible for the failure of more than one Arctic expedition In the British Arctic expedition of 1895 6 over 48 per cent of the officers and men suffered from scurvy In spite of a varied dietary Scott s polar expedition was handicapped by the disease On the other hand Peary, Shackleton, Amundsen, and Stefansson[24] were more successful the latter reports only three cases in his large party during their five years in the Arctic circle

Formerly it was the scourge of the maritime world The history of

Lord Anson's expedition of 1740 gives a graphic picture of the ravages caused by scurvy in the British navy of the eighteenth century It bore the same relationship to the mortality of the navy that typhoid and typhus fevers did to that of the army From 1851 to 1863 there were 1,058 admissions for scurvy to the hospital ship, Dreadnaught, in contrast to 580 cases during the next twelve years Owing to the more stringent regulations of the seaman's diet and to the shorter duration of the sea voyage since the introduction of steam, scurvy has almost ceased to exist in the mercantile and naval marine—almost but not quite During World War II Nelson[107] reported 64 cases of scurvy aboard a United States warship during a period of two months This represented 14 per cent of the ship's complement

Sporadic cases occur in all parts of the world under conditions which favor its development Meulengracht [6] reported 8 cases of scurvy in bachelors from Copenhagen, McMillan and Inglis[109] gave the incidence of the disease in Edinburgh between the years 1937 and 1943 as 145 cases or 0 3 per cent of medical admissions During the same period there were 244 cases in Glasgow These figures may be compared with an incidence of 0 14 per cent at the Boston City Hospital between the years 1930 and 1939 In connection with the foregoing figures it should be noted that the incidence for the years 1938-9 was not significantly higher than for the war year 1942-3

The infantile form occurs sporadically in all countries Some years ago the American Association of Pediatrics was able to collect 379 cases from American medical literature for purposes of statistical study [27] Dogramaci[108] reported 241 cases occurring at the Infants' and Children's Hospitals of Boston between the years 1936 and 1945

Two important facts with respect to vitamin C deficiency have contributed largely to the persistence of the disease commonly in a mild or 'subclinical form The first is the fact that the human body is unable to synthesize the vitamin The second is the ease with which is is destroyed Fruit and vegetables rich in vitamin C are rendered almost free of the vitamin by boiling in open vessels Even wilting of leafy vegetables reduces their antiscorbutic properties For these reasons it is now customary to 'enrich many foods, especially canned goods, by adding vitamin C in order to compensate for the loss of the vitamin during the processing

Predisposing Factors In discussing the predisposing factors it has been customary to stress the importance of unfavorable meteorological conditions such as the cold damp weather and improper sanitation

seen in the old damp poorly ventilated rooms of the crowded tenements of large cities These factors probably have been overemphasized In the Boston cases[108] the greatest number occurred during July with June and August a close second yet these months are probably the warmest and sunniest of the entire year Similarly in Edinburgh[109] the highest incidence was reported in the month of June In the light of our present knowledge of the etiology of scurvy it would seem to be primarily a matter of an abundant supply of vitamin C rich foodstuffs which are likely to be in short supply in spring months and abundant in the autumn, at which time the disease reaches its lowest incidence Excessive physical exertion experienced by the soldier or lack of proper exercise and the mental depression inevitable in protracted sieges or long sea voyages have been mentioned as contributory causes probably to an unnecessary degree Previous disease such as dysentery malaria syphilis and tuberculosis may play a role but Jaffe [8] found experimentally that suppuration tends to protect against the disease possibly because destruction of tissue liberates antiscorbutic materials though this author offers no explanation of his experimental facts

Race plays no role as both the white and the black races are subject to the disease The greater prevalence among adult males is due largely to their more exposed occupations in extensive epidemics neither sex nor age affords immunity against the disease In adults scurvy may occur in any decade but in infants the incidence rises sharply from the fifth to the eighth month falling sharply to the twelfth month after which it is almost negligible

Pathogenesis

The discovery that scurvy is caused by a deficiency of vitamin C in the diet has now been amply confirmed and is generally accepted by the profession Older theories as to its cause such as the potassium deficiency theory [9 30] the acid intoxication theory [3 33] the ptomaine poisoning theory [34 3] the specific infections theory [36 37 38] the absence of organic phosphorus theory [39] and the sodium excess theory are largely of historical interest The investigations which led up to the discovery of the lack of vitamin C as the cause of scurvy were begun by two Danish scientists Holst and Frolich [3] in 1907 These investigators found that guinea pigs fed on a diet from which green vegetables had been removed or on a diet containing dried vegetables developed the disease Using variations of the diets developed by Holst and Frolich

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Predisposing Factors In discussing the predisposing factors it has been customary to stress the importance of unfavorable meteorological conditions, such as the cold damp weather and improper sanitation

The minimum requirements of vitamin C would appear to be from *8 to 50 mg* daily for newly born infants *from 22 to 100 mg* for children and from .8 to 100 mg for the adult In terms of body weight infants require from 3 to 8 mg children from 6 4 to 7 5 mg, and adults *from 0 7 to 1 6 mg* per kilogram of body weight In the light of a recent report[117] these values are more than adequate Adults apparently require somewhat less than 10 mg daily to prevent scurvy

An interesting observation regarding the etiology of the hemorrhages in scurvy is that of Jersild[104] of Copenhagen who presented clinical evidence that these were due to a deficiency of vitamin P and not vitamin C *Vitamin* P (C $_{8}H_{36\,38}O_{17}$) *is a crystalline substance found with* ascorbic acid in paprikas hips lemon juice and other fruits rich in vitamin C It is said to evert a specific regulating influence on the permeability *of vessels Jersild claimed that patients fed on a scurvy* producing diet over long periods could be protected against the hemorrhagic features of the disease by the oral administration of vitamin P Barnes,[112] *on the other hand showed in one case at least that the hem*orrhages in scurvy could be cured by C alone without P'

The controversy would seem to have been settled by an investigation on experimental human scurvy under the aegis of the Medical Research Council The volunteers who were protected against vitamin P deficiency by plum jam showed typical hemorrhagic features of skin and gums which disappeared when C alone was added to the scurvy producing diet[117]

Morbid Anatomy

Gross Anatomical Changes Rigor *mortis occurs only to a slight* degree and decomposition takes place early Except in very protracted cases there is very little wasting of the subcutaneous fat and muscles

Hemorrhagic *effusions are the most characteristic* and constant finding and occur in the skin the subcutaneous tissues under the periosteum of the long bones and in fact to a lesser extent in almost every other *organ and tissue of the body Hemorrhagic exudates are found in the* pleurae pericardium peritoneum and joints The heart muscle often is soft and presents more or less advanced parenchymatous or fatty degeneration The ventricles especially *the right* may be hypertrophied and dilated and relative incompetency of the valves may result No positive anatomical changes of any marked character are present in the capillaries either grossly or microscopically Edema of the lungs and

Cohen and Mendel[73] and later La Mer and his associates[74] constructed experimental diets which made possible a more or less quantitative measurement of antiscorbutic activity Attempts to isolate and purify the vitamin from natural products were rendered difficult by its extreme sensitiveness to heat and oxidation However, by the year 1931 a number of independent investigators [75, 6, 77] had succeeded in concentrating the vitamin, and in the following year Waugh and King[8] succeeded in isolating it from lemons as 'hexuronic acid' This substance was found to have a protective level as high as 0 5 mg per day The structural formula of the vitamin ($C_6H_8O_6$) was established in 1933 by a number of investigators [9, 80, 81] using materials obtained from adrenal glands and paprikas The name, ascorbic acid, was suggested later by Haworth and Szent-Gyorgyi[8] to designate its antiscorbutic nature The American Medical Association suggested the third name, cevitamic acid, but the 1940 New and Nonofficial Remedies uses the name ascorbic acid Reichstein and co workers[83] in 1933 synthesized both dextrorotary and levorotary forms of the acid As already stated, the vitamin is extremely sensitive to oxidation, but when protected from oxidative processes it can be crystallized from solution in water or the lower alcohols acetone ethyl acetate, and other organic solvents The colorless crystals tend to form dense radiating clusters but may form characteristic plates or needles depending on the solvent and the rate of crystallization

In addition to clinical observations, the degree of vitamin C deficiency can be measured fairly accurately by quantitating the ascorbic acid in the urine [84, 85] The excretion of vitamin C in the urine of normal man depends primarily on the relative degree of saturation of the tissues and the immediate intake of ascorbic acid As the state of saturation is approached the quantity of ascorbic acid excreted in the urine gradually increases until at saturation a marked abrupt elevation occurs The quantity of ascorbic acid required to induce saturation is, therefore, a measure of the state of vitamin C nutrition of the patient Thus, in the scorbutic patient with depleted stores of vitamin C, the giving of a known amount of ascorbic acid and the quantitative determination of its excretion in the urine will be a measure of the degree of vitamin C deficiency Accurate methods for the determination of the vitamin C level in blood plasma and the demonstration that there is a close correlation between it and the level of intake provide a simpler method of evaluating the degree of vitamin C saturation or the scorbutic tendency [86, 87]

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infarction may occur The spleen may be enlarged and soft and may show superficial infarcts There is no distinctive lesion in the liver, though fatty infiltration is common Hemorrhage may take place at any level in the intestinal tract but congestion and hemorrhage are, as a rule, most marked in the duodenum and in the lymphoid structures of the gut At these points ulceration may occur The kidneys usually are normal, but the mucous membrane of the pelvis of the kidney the ureters, and the bladder may be the seat of ecchymoses and even erosions McCarrison[4] found the adenals to be enlarged in experimental scurvy in guinea pigs but later observers have reported adrenal atrophy due to absorption of cortical fat and vitamin C It would seem that the gland is at first swollen and hyperemic but later becomes atrophic The vitamin C content may be determined roughly by soaking the split organ in silver nitrate[88] Lesions of the gums are found only when teeth are present and are most marked about carious teeth In early cases, before secondary infection occurs the gingiva are red, swollen, boggy, and bleed readily In severe cases the swelling may be so great as to hide the teeth and make mastication painful and difficult Loosening of the teeth results from rarefaction of the alveolar bones With secondary infection the gingival epithelium bcomes necrotic with ulceration or even gangrene

Histological Changes The primary morphological changes of scurvy is shown by the experimental studies of Wolbach[47 89 90] are due to a deficiency in the intercellular substances of certain mesenchymal derivitives such as the connective tissue occurring in blood vessels and its derivatives in bones and teeth Normally the fibroblast lies in an amorphous ground substance containing either fibrils of reticulum or wavy bundles of collagen fibrils When guinea pigs are depleted of vitamin C, the fibroblasts and the ground substance appear normal, but reticulum and collagen fibrils are not formed, although they begin to appear within 18 hours after the animals are given vitamin C According to Dalldorf,[88] the intercellular material of bone osteoid tissue, and of the teeth, dentin may be altered similarly by withholding or supplying vitamin C In the teeth a substitute substance osteodentin,' which has characteristics of both bone and dentin may form in place of dentin In the bones collagen fibrils may replace osteoid tissue The degree to which these changes occur depends upon the degree of vitamin C deficiency

Bones The changes which occur in the bones in scurvy are (a) cessation of new bone formation and rarefaction of cortex of existing

bone and spongiosa (b) irregularity of outline and absorption and disappearance of cartilage columns which changes cause yielding of the bone under strain and a zone of fragmented bone trabeculae adjacent to the line of junction with cartilage the so called Trummerfeld zone (Fraenkel[46]) where actual separation by fracture may occur (c) filling of the marrow spaces of the shaft adjacent to the cartilage or trummerfeld zone if that is present with loose textured connective tissue the Gerustmark, (d) subperiosteal hemorrhages The bones most commonly affected are the costochondral junctions the distal end of the femur, the proximal ends of the tibia femur and wrist

Teeth Adult teeth in scorbutic patients show resorption and porosis of the dentin which begins about Tome s canals Where the vitamin deficiency is incomplete it may be replaced by the inferior substitute osteodentin In the pulp atrophy hyperemia and degeneration of the odontoblasts occur particularly in the perivascular zones with the formation of small cysts and foci of calcification Defects in enamel and cementum have been described by Fish and Harris[91]

Muscles The changes which occur in the muscles in severe cases are (a) fragmentation of the striated fibers and reparative effects such as multiplication of the sarcolemma (b) replacement by connective tissue poor in collagen (c) metastatic calcification (d) multiple hemorrhages

Skin In the skin the initial change in scurvy is a plugging of hair follicles by horny material in which the hair is curled or looped These blocked follicles enlarge and increase in number slowly over the upper arms the back the buttocks the thighs the calves and the shins After a time these follicles turn red Microscopically at first the redness is found to be due to congestion and proliferation of blood vessels Later extravasation of blood or actual hemorrhage occurs[117]

Symptomatology

The symptoms of adult scurvy and those of Barlow s disease (infantile scurvy) present sufficient differences to warrant separate consideration though the fundamental pathology is identical These differences are due to the fact that in the one instance we are dealing with mature tissues while in the other the disease is engrafted upon those in the process of growth and development As Hess points out the passive shielded existence of the infant as contrasted with the active and exposed life of the adult may contribute also to the differences in the

symptomatology Adult scurvy will be discussed in detail, after which the differences from the infantile type will be outlined

The most frequent and most marked lesions of scurvy are swollen deeply congested, and softened gums, petechiae, diffuse livid patches on the surface of the skin, and swelling and rigidity of the hamstring muscles In severe and advanced cases there may be bleeding from the nose, mouth, and from the internal organs

Prodromata The onset is insidious and usually marked by asthenia, mental apathy, and lassitude The color becomes sallow or muddy, the eyes sunken and encircled by dark rings There may be fleeting pains in the joints, edema of the ankles, breathlessness, and constipation more frequently than diarrhea A mild degree of fever usually is present.

Changes in the Gums When teeth are present, the changes in the gums are the most striking symptoms of the disease, but edentulous gingivae may show no lesions even in well developed cases There is at first swelling of the gum around the incisor teeth or around one or more carious molars This swelling may lead to such overgrowth that the gum sends down finger-like prolongations between the teeth, often to the cutting edge The gums are bluish or purplish in color and bleed readily Ulceration may follow with a resulting discharge of very foul sanguinous fluid The teeth may become loose and fall out due to defective cementum and atrophy of the alveolar bone Occasionally the characteristic gum lesions may be absent even in well developed cases A scorbutic observed at the Montreal General Hospital showed an extensive purpuric eruption, scurvy scleroses in the muscles, and a zero ascorbic acid level in the blood, yet the teeth were firmly embedded, and the gums, though dirty and infected, showed no gross lesions of the disease It is of interest in this regard that the experimental human case [10] also showed no gross changes in the gums or teeth

Finger Nails The nails may turn brownish yellow, become loose, and even be partially or wholly shed, onychia scorbutica

Hemorrhages Stress modifies to a great extent the site and extent of the hemorrhagic lesions and the involvement of the various structures of the body For example an infant lying in a crib will develop cutaneous lesions at points of pressure, the blacksmith in the shoulders and arms, while soldiers are prone to develop hemorrhages in the calf, the hamstring, or lumbosacral muscles

Cutaneous hemorrhages occur as petechiae especially around the hair follicles of the outer and anterior aspects of the thigh and legs, which are most subject to the friction of the clothes These petechia fade in

the course of a week to greenish yellow spots which in turn disappear and are followed by a slight desquamation The tendency to cutaneous hemorrhage may show itself also as small nodules acne scorbutica or as small vesicles filled with a sanguinolent fluid herpes scorbutica or in other cases as large vesicles filled with bloody fluid pemphigus scorbuticus *In rare cases vibices or streaked extravasation of blood may* occur Larger cutaneous hemorrhages are commonly found as well as ecchymoses which may vary in size from one half to five centimeters in diameter They are bluish black in color and may occur spontaneously though more often as a result of slight trauma

In severe cases one may see ulcers usually though not always the *result of pemphigus scorbuticus These ulcers may spread rapidly* invade the surrounding tissue and lead to fatal hemorrhage They are covered usually with a tough brownish red or black scab the removal of which reveals a foul ulcerating surface covered with spongy hemorrhagic granulations and emitting a highly offensive odor They are surrounded generally by a broad halo of a dirty violet color and show little tendency to cicatrize The skin over the outer surfaces of the limbs feels dry and rough owing to the elevation of the hair follicles Edema of the feet and ankles is very frequent and may be very marked though not always pitting on pressure

Subcutaneous and muscular hemorrhages are not uncommon in the hamstring muscles of the thigh and in the calves where they give rise to the characteristic brawny induration known as the scurvy sclerosis The skin over such an area is red shiny and hot while there is marked pitting on pressure which persists longer than in edema from an ordinary serous transudate Such effusions also occur at the bends of the elbows around the malleoli and beneath the masseters where they interfere with the normal movements of the joints and cause a pseudo-ankylosis

Subperiosteal hemorrhages are common about the femur the tibia and to a lesser extent the radius, ulna and scapula The resulting peculiar *fusiform swellings extend from the epiphyseal line towards the shaft* They are boggy to touch though the skin over them may be tense and shiny On palpation crepitus may be elicited if fracture or epiphyseal separation is present Rarely as in a case reported by Taylor[48] the periosteal hemorrhage may occur about the lumbar vertebrae and suggest Pott s disease Proptosis due to orbital hemorrhage has occurred not infrequently The bleeding usually takes place between the orbital plate of the frontal bone and its subjacent periosteum

symptomatology Adult scurvy will be discussed in detail, after which the differences from the infantile type will be outlined

The most frequent and most marked lesions of scurvy are swollen, deeply congested, and softened gums, petechiae, diffuse livid patches on the surface of the skin, and swelling and rigidity of the hamstring muscles In severe and advanced cases there may be bleeding from the nose, mouth, and from the internal organs

Prodromata The onset is insidious and usually marked by asthenia, mental apathy, and lassitude The color becomes sallow or muddy, the eyes sunken and encircled by dark rings There may be fleeting pains in the joints, edema of the ankles, breathlessness, and constipation more frequently than diarrhea A mild degree of fever usually is present

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substance fusing the endothelium The bone marrow in cases of scurvy has been reported as normal[110] or hypoplastic[113, 114]

Circulatory Symptoms The pulse may be rapid and feeble in the later stages of the disease The heart commonly is enlarged, and usually there are hemic murmurs Darling[23] noted right sided hypertrophy and degenerative changes in the vagus and all its branches while records of fatty degeneration and dilatation of the organ are fairly common Hess believes that the cardiac manifestations of the disease have not been emphasized sufficiently Sato and Nambu[16] also found hyperemia and atrophy of the muscle fibers and increase in the connective tissue

In a group of 20 human volunteers[117] on a vitamin C free diet for many months two developed cardiac symptoms which disappeared promptly when given large doses of the vitamin These two patients did not know whether they were controls or not The cardiac pain and electrocardiographic changes (high ST in leads I and II in one and heartblock in the second) were found to be reversible within a few hours of the administration of large doses of vitamin C These observations strengthen Hess belief that cardiac manifestations of the disease are not uncommon

Urine The urine is at first scanty high colored turbid and may contain albumin As improvement occurs it becomes more abundant and pale A sudden diuresis may follow the administration of orange juice One of the most constant abnormal features is blood, which usually emanates from the kidneys though it may originate lower down in the urinary tract O Shea[64] reported hematuria in 15 per cent of his adult cases Pyuria usually is a manifestation of secondary infection Abnormal values for the various mineral elements of the urine reported by the early investigators of the disease were not confirmed by the more detailed studies of Baumann and Howard[31] The latter studies were carried out on cases of human adult scurvy and on experimental scurvy in the guinea pig and monkey

Gastro intestinal Symptoms One of the earliest as well as one of the most constant symptoms of scurvy is a lack of appetite and this is especially true of latent cases Rarely bulimia and marked capriciousness of the appetite are encountered in adult scurvy The underlying basis for the anorexia is unknown but hyperchlorhydria has been noted Gastric acidity usually is normal or low but achlorhydria has been reported[109] It is of interest that Ahlmann[72] and also Voegtlin[7] have shown that water soluble vitamin acts as a powerful stimulant of gastro intestinal secretions

Hemmorrhages from the mucous membranes are common, especially from the nose and mouth When there is much diarrhea, melena also occurs Hemoptysis, hematmesis, and hematuria are rare in the adult form, though the latter occurs in 33 per cent of infantile cases, according to Kinkelstein,[49] and may actually lead to nephritis[50] Menorrhagia, metrorrhagia, hemoperitoneum, and hemorrhagic effusion into the pleurae and pericardium have been reported occasionally

Blood and Blood-forming Organs Scurvy in adults usually is associated with anemia, though it is much less common in infants It was moderate or slight in 40 of 53 cases reported by McMillan and Ingles[109] and present in all but two of nineteen reported from The Cincinnati General Hospital[110] There is a growing belief[93,94] that the anemia in scurvy results from a deficiency of factors other than ascorbic acid in the scurvy-producing diet, although Spies and his co workers[110] found that the addition of vitamin C alone to the deficient diet cured the anemia in nine of their cases The anemia is nearly always of the normocytic type Only two of the Edinburgh series of 53 and a minority of the 19 severe Cincinnati cases showed a macrocytic anemia On the other hand, Gottlieb[111] has reported 4 cases of macrocytic anemia in severe cases all of whom became normal on ascorbic acid therapy alone In infants as Hess has shown, the hemogram may reveal a polycythemia

Experiments with guinea pigs rendered scorbutic by a 'C'-deficient diet show that anemia does not develop unless the iron intake is inadequate, an observation which has been confirmed in clinical cases of scurvy by Abt and Farmer[9] It would seem likely that anemia in scurvy is not directly due to vitamin C deficiency but to the hemorrhages, associated infections, or iron deficiency in the diet

The leucocytes and leucocyte formula in scurvy usually are normal or depressed unless secondary infection occurs The blood platelets may be normal or moderately reduced Severe degrees of thrombocytopenia are encountered rarely The bleeding and coagulation times usually are normal, although instances of prolongation of the latter have been reported[5] Retraction of the clot is normal

Weakening of the capillary wall may be demonstrated by the tourniquet or Hess or Rumpel-Leede test It is invariably positive in the active phase of the disease This damage to the capillary wall is not evident on histological examination It is not known whether the weakness occurs in the collagenous sheath about the endothelium or in the cement

former up to 200 and the latter to 60 The pulse is astonishly labile increasing markedly with exertion excitement or a rise in temperature, which is not uncommon That these manifestations are due to scurvy per se is shown by the spectacular and complete subsidence under antiscorbutic therapy

The diagnosis of latent infantile scurvy is based mainly on the reaction to specific therapy and on a history of prolonged feeding with pasteurized milk These cases may show pallor anorexia increased reflexes and the cardiorespiratory syndrome Hess states that this type of the disease is now the most common form especially in large cities where the entire milk supply for infants is pasteurized The vitamin C loss as a result of pasteurization of milk depends upon the method employed By the widely used holding method a loss of from 20 to 30 per cent is not uncommon Less inactivation occurs as a result of the short time high pressure process if the milk does not come in contact with copper pipes When the extreme sensitivity of the vitamin to heat and oxidation is recalled it is not surprising that the infant s formula based on pasteurized milk and later subjected to aging reheating and diluting, has a very low antiscorbutic value by the time it reaches the infant In all three types of infantile scurvy during the active phase of the disease the growth impulse as a rule remains in a quiescent state though in some cases normal growth takes place

Subclinical Scurvy

The recognition of vitamin C deficiency in the blood plasma and in urinary excretion has led to the segregation of cases which present insufficient clinical evidence upon which to base the diagnosis but which are none the less instances of latent scurvy Such cases occur infrequently in Montreal among indigents who cannot provide fresh fruits during winter months The prolonged strict ulcer regime has also been known to lead to a state of mild vitamin C deficiency These subclinical cases of scurvy complain of weakness and lassitude for a period of two to three weeks followed by petechiae or ecchymoses of skin or mucous membranes Appropriate tests will show diminished capillary weakness The fasting blood plasma will reveal a subnormal vitamin C concentration The degree of vitamin C unsaturation may be determined by measurements of the blood concentration and urinary excretion after a test dose of ascorbic acid During this period radiographic or other changes in the bones may not be recognized and the

In severe cases the tongue may become swollen and later dry, hardened, and encrusted. Among adults stomatitis frequently develops on the basis of malnutrition and may occur in epidemic form as among large bodies of troops.

Constipation is the rule, but diarrhea of a dysenteric type may be present. The stools in simple cases consist largely of partially digested food and blood stained fluid, but in the more dysenteric type may be hemorrhagic or even contain large clots of blood.

Nervous System Symptoms. Apart from languor and mental depression verging upon melancholia, there may be delirium and even deep coma or epileptiform convulsions and hemiplegia. These are dependent upon hemorrhages into the brain as described by Opitz, Hess[5] and Sammis. On the other hand one reads with interest from Lord Anson's narrative of his voyage that 'many of our people, though confined to their hammocks, ate and drank heartily, were cheerful and talked with much seeming vigor and in a loud strong tone of voice.' The knee kicks may be increased, and there may be hyperesthesia of the limbs. The optic discs usually are pale with occasional signs of neuroedema. Nyctalopia, a frequent symptom, should be considered as of circulatory rather than of nervous origin.

Differences in Symptomatology of Infantile Type

Scurvy in infants, when advanced, presents essentially the same syndrome as in the adult but such a picture is clinically uncommon. For descriptive purposes the infantile cases may be divided into acute, subacute, and latent.

Children with acute infantile scurvy generally are poorly nourished, pale, with a peculiarly alert and worried expression. The child lies on its back and screams if approached, owing to fear of manipulation of the swollen and exquisitely tender limbs. There are usually no skin manifestations but if teeth are present the gums may be swollen, purplish, and bleed readily.

The subacute form is met with more commonly. It occurs usually in the second half of the first year of life. The child has not gained weight, it is pale, irritable, peevish, with capricious appetite. The changes in the gums and the tender limbs, noted in the acute forms, are present, and here and there over the body petechial spots may be found. Of special importance is what Hess calls the cardiorespiratory syndrome. The heart and respiratory rates are unusually rapid, the

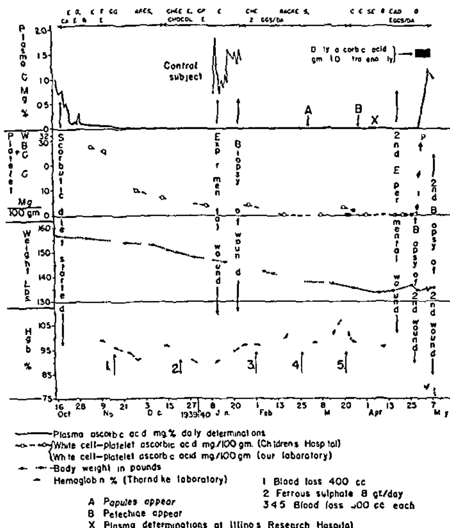


FIG 1 Graph of pertinent data in a case of experimental human scurvy

fell to zero shortly before the appearance of clinical scurvy

Adequate wound healing occurred after the plasma ascorbic acid had been zero for forty four days and when the white cell platelet ascorbic acid level was 4 mgm per 100 c c

With total vitamin C deficiency failure of wound healing occurred

gums present no lesion As the degree of vitamin C unsaturation increases, larger hemorrhages and hematomas make their appearance, and early skeletal changes may be present [97] Sloan[96] reported 18 cases of scurvy in young children undiagnosed clinically or at routine necropsy yet all had distinct lesions Oehnell,[116] studying cases of vertigo in Stockholm, observed 87 due to scurvy Of these, 45 suffered from clinical scurvy, 8 from probable scurvy and 34 from subclinical scorbutus His criteria for the diagnosis of scurvy were (a) history of a scorbutic diet, (b) a positive capillary resistance test which disappears after ascorbic acid therapy, (c) denticulosis as shown by X ray picture of the dental pulp (d) a low ascorbic acid level in the blood and (e) improvement after ascorbic acid therapy The disease, therefore, should be considered wherever a history of vitamin C dietary deficiency exists and appropriate chemical and biological tests should be carried out

Experimental Human Scurvy

Much light is thrown on the various problems of the etiology, pathogenesis, and symptomatology of clinical and subclinical scurvy by the studies of Crandon Lund and Dill[105] and Lund and Crandon [106] Crandon remained for six months on a diet totally deficient in vitamin C while receiving daily 30 000 international units of vitamin A 132 units of vitamin B, and 80 micrograms of riboflavin fortified by 10 Harris yeast tablets 50 mgm nicotinic acid 5 280 units of vitamin D and after the 2nd month, 4 c c of wheat germ oil The pertinent data of this investigation[105] is shown in Fig 1 In this experiment, multiple avitaminoses, infection, growth or other stresses were excluded, and the data give the effect of C avitaminosis of six months' duration on a human male and not on a guinea pig, rabbit, or other lower animal The results are summarized by these investigators[105] as follows

One hundred and thirty-two days of a diet totally deficient in vitamin C were required for the first abnormal clinical signs—hyperkeratotic papules—to appear 161 days were necessary for the appearance of the perifollicular hemorrhages of scurvy

'The plasma-ascorbic acid level was zero for thirteen weeks before the first evidence of clinical scurvy was manifest It is not necessarily therefore, a good index of the vitamin C status of the individual

'The vitamin level in the white-cell platelet layer of the centrifuged blood was a good index of the vitamin C status of the subject This level

Twenty volunteers nineteen men and one woman were placed on an adequately vitaminized diet with the exception of C' All received tablets daily but not all tablets contained the vitamin The controls were not known to the volunteers or to the observers Ten received no vitamin C Seven received 10 mgm and three 70 mgm daily The course of events in the ten who received no vitamin C was as follows

(1) For 17 weeks no clinical signs
(2) After 17 to 21 weeks hyperkeratosis of hair follicles
(3) After 26 to 34 weeks perifollicular hemorrhages
(4) After 30 to 38 weeks swelling and hemorrhages of the gums
(5) Failure of wound healing only after other clinical signs of scurvy

At no time were the following noted anemia dryness of the skin, night blindness, changes in the plasma proteins or phosphatase This group of investigators[117] found that the minimum amount of vitamin C necessary to protect against scurvy or cure it was much less than formerly believed They placed the level at about 10 mgm daily which is a much lower figure than is commonly accepted as a minimum

Complications

The pulmonary are the most common of the complications of scurvy and of these pneumonia is by far the most frequent Gangrene of the lung may occur in severe cases and is evidenced by dyspnea, expectora tion of dark foul sputum and a fatal termination That hemorrhage into the lung substance may be confused with pneumonia was noted by Buzzard[30]

According to Barlow[11] the sternum and costal cartilages may sink in and present a most curious chest deformity In his article in Keating s Encyclopedia he described such a case in which there seemed to have been multiple fractures of the sternal end of the ribs while the costal cartilages appeared to have sunk back away from the ribs so that they with the sternum were on a plane posterior to their normal situation Blau[17] Bofinger [6] and Darling[53] have noted a similar condition in adults Night blindness hemeralopia may occur early in the disease in those who have been much exposed to a bright light as in arctic exploration or in maritime duty in the tropics Night vision nyctalopia, also may occur They are both apparently the result of the anemia and exhaustion and are not restricted to scurvy According to Kitamura there are only 14 cases in the literature in which changes in the eye grounds were found and in only eight of these were there proven retinal

The tissues under these circumstances showed microscopically a lack of intercellular substance Parenteral vitamin C alone brought about good healing, and considerable intercellular substance appeared within ten days

'Hyperkeratotic papules containing ingrown hairs appeared over the buttocks and posterior aspects of the legs as a result of vitamin C deficiency, indeed, they may be the first sign of such a deficiency

'There were no gross changes in the gums or teeth (with good pre existing oral hygiene) Although the mouth was grossly negative, X-Ray films of the teeth showed interruptions of the lamina dura in early acute scurvy Such an X-ray picture may be one of the better diagnostic criteria in early scurvy

Vitamin C deficiency did not produce anemia

'After prolonged vitamin C deficiency there was inability to perform aerobic work, although the capacity for anaerobic work was undiminished After a period of aerobic work in the scorbutic state the rate of disappearance of the blood lactate was abnormally slow

During a six-month period of total deficiency and after a month of clinical scurvy the blood complement titer was still normal Over this period there was no evidence of lowered resistance to infection

'The Gothlin, Dalldorf and Rumpel Leede tests were negative, even in the presence of frank scurvy These tests must, therefore, be poor indices of subclinical scurvy, even though they may in some cases produce petechiae which are cleared up by ascorbic acid therapy

With severe vitamin C deficiency there was a fall in the blood pressure

'There was a lowering of the total phosphorus content of striated muscle, with an increase in the phosphagen phosphorus

'All the signs and symptoms of scurvy rapidly disappeared following the intravenous injection of ascorbic acid

'When the state of deficiency was complete, the plasma ascorbic acid level fell to zero in five hours after injection of 1 gm of the vitamin

'Although the blood became completely saturated (as measured by plasma saturation curves and white-cell-platelet levels) after 3 or 4 gm of ascorbic acid had been given intravenously, the tissues were not completely saturated at this time, since the urinary output of ascorbic acid was still well below maximal over a six-hour period'

The pioneer observations on human experimental scurvy by Crandon and his co-workers have been amplified by those of a group of investigators working under the aegis of the Medical Research Council

Differential Diagnosis

In adults thrombocytopenic purpura, acute leukemia, and mercurial poisoning deserve consideration The gum lesions of scurvy may be simulated closely by Vincent s Infection or the two conditions may co exist[115] Essential thrombocytopenic purpura or morbus maculosus Werlhofii may be distinguished by the absence of characteristic gum lesions and the blood changes in the primary blood dyscrasia, which are prolonged bleeding time absence of clot retraction and thrombocytopenia The capillary resistance test will likely be positive in both conditions Acute leukemia especially the aleukemic type may be differentiated by the blood picture in this disease or failing a characteristic hemogram, by a smear from the sternal marrow Acute monocytic leukemia is especially prone to produce gum lesions almost indistinguishable from scurvy It may be recognized readily as such by examining sternal marrow smears Mercurial poisoning may resemble scurvy closely even to the cutaneous hemorrhages but the pronounced toxic degenerative renal lesions are seldom encountered in scurvy Salivation a feature of mercurial poisoning is not present in scurvy In the infantile form rickets rheumatism infantile paralysis syphilitic osteitis, and osteosarcoma may be suggested

Rickets may co exist with true scurvy, which in part accounts for the former confusion of the two diseases Even with modern clinical and histological methods Schoedel and Nauwerck[60] found evidence of rickets in 21 of 40 fatal cases of scruvy The craniotabes square head and bossed skull the rosary the swollen wrists and the bowed tibiae are the characteristic stigmata of rickets

Rheumatism frequently is diagnosed because of the tender swollen areas about the joints of the lower extremities The joints themselves are free however and the presence of the swollen gums and the dietetic history should clear up the diagnosis Infantile paralysis may be suggested by the motionless attitude of the legs and the marked degree of hyperesthesia In this disease however there is no swelling of the affected limb and the other scorbutic stigmata are absent Syphilitic osteitis may give some difficulty in infancy though the history of a possible syphilitic taint and the Wassermann reaction will differentiate clearly the two conditions Osteosarcoma has been diagnosed occasionally and even an amputation performed The presence of the other signs of scurvy however should render such a mistake impossible

hemorrhages He reports a case in which postmortem there was a marked edema of the retina with hemorrhages and a circumscribed ganglionic hypertrophy of the nerve fibers

Schreiber [8] and others mention dysentery as a complication of scurvy epidemics during World War I Where there is marked involvement of the nervous system and especially if there is aphonia indicating involvement of the recurrent laryngeal branch, the association of beriberi should be considered Although rare, a true nephritis may occur during the course of the disease The urine may be loaded with albumin and casts but these disappear rapidly under antiscorbutic treatment

One of the most common complications of scurvy is secondary infection, which may manifest itself as a pyelitis, as a cervical adenitis following gingival pyorrhea, as a 'bubo' of the groin following infection of the lower extremity, or as an abscess of the calf of the leg following hemorrhage in this region Aschoff and Koch have laid emphasis on the frequency with which diphtheria complicated scurvy among soldiers

Diagnosis

The diagnosis of scurvy presents no difficulty when the disease has developed fully The swollen gums, the cutaneous hemorrhages, the capillary weakness and the bone changes following upon a history of poor hygiene and a diet deficient in vitamin C are adequate proof of the presence of the disease In infantile cases the diagnosis presents more difficulty owing to the paucity of clinical signs, but the X ray findings usually are characteristic According to Bromer,[59] early cases show (a) a ground glass appearance of the shaft of the bone especially near the diaphyseal ends, (b) broadening of the dense zone of temporary calcification at the very end of the shaft shadow, (c) a pencil point thinning of the cortex of the shaft, (d) a dense ring about the epiphyseal center of ossification (Wimberger's sign) As the disease progresses, a zone of decreased density occurs just behind the broadened dense zone mentioned under (b) and subperiosteal hemorrhages make their appearance Later still, separation of the epiphyses may be noted In subclinical cases, where characteristic clinical or radiological changes are lacking, but where a possible dietary deficiency exists or in infantile cases lacking a well-developed clinical picture, the diagnosis should be put to the proof by estimation of the ascorbic acid content of blood plasma and urine both before and after the giving of a test dose of the vitamin

Prophylaxis The prevention of scurvy depends upon an adequate intake of vitamin C in the diet The exact requirements for normal health are not known They vary considerably with age pregnancy lactation, and disease It would seem likely that the quantities of the vitamin commonly regarded as adequate to prevent the disease are much lower than those which should actually be taken Experimental studies on guinea pigs have shown that about twice as much vitamin C is required to prevent the first appearance of microscopic alterations in the teeth as to prevent the visible symptoms of scurvy Comparable observations have been recorded in infants and children [100]

The diet of a normal adult should contain from 600 to 1 200 international units equivalent to from 30 to 60 mg of vitamin C per day or in terms of fresh orange lemon, or tomato juice about 100 c c For artificially fed infants up to the age of 3 or 4 months from 5 to 15 mg of ascorbic acid daily 10 to 30 c c orange juice is considered by the Technical Committee on Nutrition of the Health Organization of the League of Nations to be the physiologically indispensable minimum During pregnancy and lactation about three times the normal adult requirement is advisable

Treatment

The treatment of the disease either in the subclinical or full blown state may be hastened by the giving of ascorbic acid in addition to a diet rich in vitamin C The therapeutic dose of crystalline vitamin C is about 30 mg daily for infantile scurvy and proportionately larger doses for adults Ascorbic acid is freely soluble in water and may be administered orally in tablet form or dissolved in water For parenteral use Fisher and Leake[10] have recommended that ascorbic acid be dissolved in sterile water and neutralized with one half of its weight of sodium bicarbonate immediately before injection to prevent local reaction In some instances where the crystalline ascorbic acid is given by mouth from ten to twenty five times the normal dose must be given to produce the desired therapeutic effect This appears to be due to faulty absorption and destruction in the gut Kendall and Chinn[103] have shown that ascorbic acid is destroyed by certain bacteria isolated from stomach and intestinal contents of achlorhydric patients The vitamin is nontoxic even in large doses Repeated doses of as much as 6 gm have been administered intravenously to adults without toxication [93]

Prognosis

The course is ordinarily a subacute or chronic one lasting from four weeks to four months, even in favorable cases Partial ankylosis of the joints sometimes occurs as a result of extensive hemarthrosis, and patients may be subject to pain and stiffness of the joints for many years afterwards The ultimate prognosis, however, is good, if the disease be recognized and early treatment instituted There is no greater therapeutic miracle than that exemplified by the response of scorbutic symptoms to the correction of the diet In severe, longstanding cases the condition of the lungs and heart muscle may exert an unfavorable influence Further, the occurrence of a pulmonary complication, as gangrene, or the development of some intercurrent disease may seriously imperil the patient's life Occasionally a fatal hemorrhage from one or another of the mucous membranes may occur

The usual cause of death in uncomplicated cases is syncope According to Smith[61] the mortality in the Seaman s Hospital at Greenwich was only 1 83 per cent among the 816 cases admitted in the past fifty years Thompson[6] quotes Berthensen's figures from an epidemic in 1891 in a military hospital of St Petersburg of 225 patients, 8 5 per cent died and 25 per cent of the survivors had to be given an entire year's furlough on account of anemia and weakness

Prophylaxis

Historical The superlative value of the citrus fruits as antiscorbutics has long been recognized The addition of lime juice to the dietary of the British Navy practically eliminated the disease from the personnel of that service Even in tablet form lemon juice was found by Bassett Smith[64] to preserve its efficacy for at least three months Bottling, however, is apt to destroy its potency through decomposition into free citric acid and carbonates The value of malt as an antiscorbutic was recognized by Foster who accompanied Captain Cook on many of his voyages According to Dyke,[1] Kaffir beer, which is made from germinated millet, has been used for many years to avert scurvy in mines and prisons in South Africa Modern methods of malting and brewing are said to remove all the vitamin C from beer It is of interest that the North American Indians taught the French immigrants the antiscorbutic value of a decoction which they called 'ameda derived from the arbor-vitae tree (Parkman[63])

The fortification of canned fruit and vegetable juices by the addition of ascorbic acid, now common practice adds materially to their vitamin C content and their value as antiscorbutic foodstuffs

Treatment of the Anemia

Where anemia is present full doses of iron in the form of ferrous sulphate 1 gm (gr 15) should be given daily

Local Treatment

Antiseptic mouth washes such as potassium permanganate potassium chlorate Dobell s solution etc should be used in all cases The gums may be painted with a 10 per cent solution of silver nitrate or 5 per cent chromic acid Gentle massage will aid in the absorption of the brawny induration while passive motion of the joints often is indicated

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Vitamin Content of Foodstuffs

The vitamin C content of many every-day foods is high, but so sensitive is the vitamin to heat and oxidation that many vitamin C-rich foods are rendered almost inert before ingestion For instance, Bessey states that crushing or bruising of many vegetables such as spinach, cabbage, turnips, and rutabagas causes liberation of enzymes, oxidases which in the presence of air catalize the oxidation of ascorbic acid He states that this reaction is so rapid that it may lead to the complete inactivation of the injured tissue in a few minutes Shredding of vegetables as in preparing salads leads to a rapid decrease in vitamin C content Pickling, salting, curing or fermenting usually results in complete loss of vitamin C Boiling in an open vessel soon destroys all vitamin C content This destructive process is rapidly complete, if the vessel is of copper, or if an alkali such as soda is added to maintain color in vegetables such as peas and spinach It is of practical importance that orange, tomato, and grapefruit juices, even after canning, are rich sources of vitamin C, although other canned fruits such as cooked apricots, peaches, plums, and cherries are practically inert in this respect [99] In spite of the fact that milk is the most nearly perfect and least dispensable food, it is poor in the antiscorbutic vitamin Fresh raw cow s milk contains from 2 to 2 5 mg of ascorbic acid per 100 c c, or roughly twenty times less than an equal quantity of orange juice It is from 4 to 6 times less potent in this respect than mother s milk It should be recalled that pasteurization further reduces the 'C content by from 30 to 60 per cent unless unusual precautions are observed [101]

The following vitamin C values for fresh and canned fruits and vegetable juices are of interest [11]

Juice	*Vitamin C in mg per c c*	*Juice*	*Vitamin C in mg per c c*
Lemon fresh	0.455	Peach fresh	0.018
Orange fresh	0 500	Plum fresh	0.030
Orange canned	0 294	Rhubarb fresh	0 278
Tangerine fresh	0 208	Sauerkraut	0 082
Lime fresh	0.459	Cabbage fresh	0.427
Grapefruit fresh	0 266	Pepper fresh	0 203
Grapefruit canned	0 150	Carrots fresh	0.040
Pineapple fresh	0 310	Celery fresh	0.009
Pineapple canned	0.0-0	Turnip fresh	0 191
Tomato fresh	0 242	Cucumber fresh	0.012
Tomato canned	0 157	Potato fresh	0.021

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CHAPTER XI-A

ACRODYNIA

By KENNETH D BLACKFAN AND CHARLES F McKHANN

Table of Contents

Introduction

Acrodynia is a clinical entity characterized by the development of painful red swollen hands and feet tachycardia hypertension hypomotility mental apathy anorexia and photophobia The onset is insidious the duration months and unless terminated by an intercurrent infection the outcome is favorable

Although first described in 1903[1] the syndrome escaped attention until recent years when it was recognized independently in widely separated geographical locations and designated by a number of descriptive titles

Among the names which have been applied to this bizarre condition some at least should be mentioned trophodermatoneurosis (Selter) 1903 erythroedema (Swift) 1914 Swift s disease pink disease (Clubb) acrodynia (Weston) 1920 polyneuritic syndrome resembling pellagra (Byfield) 1920 vegetative neurosis (Feer) 1923 Feer s disease (Erickson) dermatopolyneuritis (Thursfield)

The first series of cases to receive prominence was that reported by Swift in 1914 in Australia[2] Not until 1920 were descriptions of the disorder published in the United States[3,4] In Europe the first description appeared in the literature in 1921[5] The studies of Feer in 1922 and subsequently are of outstanding importance[7]

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merous cases in certain areas and none in neighboring equally populous regions has been used as presumptive evidence of the infectious nature of the malady The lack of reported cases in certain areas may be due to failure of recognition of the condition Even if a real disparity in incidence is encountered it may be attributed to lack of a regional dietary factor as well as to infection Although infections are demonstrable in patients suffering from acrodynia they may be assumed to be of secondary importance

The chronicity of the disease the failure of association with other deficiency disorders and failure of experimental production of the syndrome cast serious doubts on the theory of dietary deficiency as the specific etiologic factor of acrodynia

Suggestions have been made that acrodynia is due to a lack of minerals in the diet that it is due to excessive sunlight[6] or that it is a type of encephalitis[17 18 19] perhaps following influenza Similarities of acrodynia to ergotism[0] and to pellagra[2, 0] have been pointed out Despite the efforts of numerous investigators to cast some light on the subject the etiology and pathogenesis of acrodynia remain obscure

PATHOLOGY

Pathologic studies of patients with acrodynia are not extensive In cases that have come to autopsy the immediate cause of death has been a terminal infection usually of the respiratory system The skin is the site of chronic erythema with hyperkeratosis hypertrophy of the epidermis and sweat glands and slight pigmentation of the rete[21] Evidences of chronic inanition are usually present throughout the body and especially in the gastro-intestinal tract The lymphatic hyperplasia frequently noted may be due to the specific cause of the disease to the inanition or to the secondary infection

Various studies of the nervous system indicate that there is a widespread peripheral nerve degeneration with demyelinization of the nerve sheaths[~ 23 4] Cellular infiltrations have been described in the spinal cord and in the nerve roots extending as high as the base of the brain. Careful examination of the brain stem has yielded little information beyond evidences of edema and slight meningeal irritation The suggestion has been made that the findings in the nervous system are entirely explainable on the basis of response to terminal infections elsewhere in the body or that they are post mortem or agonal changes and so not specific for acrodynia

It must be concluded from a survey of the reported pathologic findings that acrodynia although a clear-cut syndrome does not present at post mortem examination a characteristic or diagnostic disease picture sufficiently extensive to explain the widespread and severe symptoms

Etiology

The disease is primarily one of infancy and early childhood Sex does not appear to be a factor In the accompanying table is shown the age distribution of the forty four patients observed in this clinic (Table I)[8]

TABLE I

Age Incidence *

Under 1 yr	12
1–2 yrs	13
2–3 "	7
3–4 "	6
4–6	4
Over 6	2
Females	24
Males	20

* Cases of Acrodynia observed at the Children s Hospital Boston from 1924 to 1932

The seasonal incidence is perhaps not readily determinable in this as in other diseases of gradual onset and prolonged course Although cases have been observed in all seasons of the year, a higher incidence in the winter and spring months has been indicated in the majority of the larger groups reported

In 1828 there occurred in Paris an outbreak of a disease whose manifestations simulated in many respects the characteristic features of acrodynia[9] This disease, which appeared in large numbers of the population, was ultimately attributed to poisoning with arsenic Unlike the disease which at present carries the name acrodynia the Paris outbreak was confined largely to adults However it was from a study of the reports of this early outbreak and the assumption that the present disease was of similar nature that led to the adoption of the name, acrodynia, the term which had been applied to the Paris disease and which means "painful extremities

An erythroedema due to arsenic has been described which simulates acrodynia but which lacks many of the characteristic features of the disorder However the possibility that arsenic is the specific etiologic agent of acrodynia continues to be suggested[10,11]

Prominent among the current views regarding the etiology of acrodynia are that the disease is due to infection[3,1] or dietary deficiency[13,14,15]

If the disease were due to an epidemic type of infection, variations in incidence should occur from year to year This has not been found to be the case Also transmission of the disease to other members of a family has been encountered very rarely The geographical distribution of the disease, with nu

merous cases in certain areas and none in neighboring equally populous regions, has been used as presumptive evidence of the infectious nature of the malady The lack of reported cases in certain areas may be due to failure of recognition of the condition Even if a real disparity in incidence is encountered it may be attributed to lack of a regional dietary factor as well as to infection Although infections are demonstrable in patients suffering from acrodynia they may be assumed to be of secondary importance

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Various studies of the nervous system indicate that there is a widespread peripheral nerve degeneration with demyelinization of the nerve sheaths[22,23,4] Cellular infiltrations have been described in the spinal cord and in the nerve roots extending as high as the base of the brain Careful examination of the brain stem has yielded little information beyond evidences of edema and slight meningeal irritation The suggestion has been made that the findings in the nervous system are entirely explainable on the basis of response to terminal infections elsewhere in the body or that they are post mortem or agonal changes and so not specific for acrodynia

It must be concluded from a survey of the reported pathologic findings that acrodynia although a clear-cut syndrome does not present at post mortem examination a characteristic or diagnostic disease picture sufficiently extensive to explain the widespread and severe symptoms

Symptoms

The onset of acrodynia is insidious Frequently the mother cannot state accurately when the disease began, although in some instances an upper respiratory infection either initiates the symptoms or quickly becomes an associated process The infant or young child gradually becomes irritable, fretful and sleepless and refuses food Cessation of growth and progressive loss of weight ensue Profuse sweating lacrimation and photophobia with excessive secretions from the nose and throat develop The cheeks are bluish red in color with the tip of the nose in many cases, very red The expression of the suffering patient is worried and unhappy Ulcerations of the mucous membranes of the mouth are of frequent occurrence Sooner or later hyperemia alternating with ischemia appears on the hands and feet The palms and soles develop a dull beefy red frost bitten appearance and although the infants show evidence of marked discomfort and older children complain of intense burning and itching in these locations the extremities usually feel cold and clammy Maceration of the skin of the palms and soles occurs followed by desquamation and frequently secondary infection Rashes of the papular type, which itch intensely may appear over the whole body There is a wide variation in the intensity or severity of the cutaneous lesions and it seems quite possible that a patient may suffer from acrodynia and present minimal skin lesions

The patient tends to assume abnormal positions in bed frequently placing himself in the knee chest position with his head burrowed in the pillows This position has been attributed to the photophobia but as older children with the disease often complain of abdominal cramps we are inclined to believe that even infants may assume this position in an attempt to relieve abdominal discomfort

Except as the result of secondary infection the temperature in acrodynia is not elevated

Physical examination reveals fundamental circulatory disturbances even in early cases often before the appearance on the hands and feet of the typical vascular changes Signs of the circulatory involvement are tachycardia and an elevation of the blood pressure The pulse rate varies usually between 140 and 200 per minute and is little influenced by cry effort or sleep The rhythm is regular The electrocardiogram shows no abnormality except the tachycardia Hypertension is present to some degree in all cases and is said by Feer to be the most constant sign of the disease

In addition to the features mentioned above symptoms referable to the central nervous system with profound mental disturbances frequently appear early and persist throughout the course of the disease Lassitude apathy, irritability and disturbances of the sleep rhythm together with diminished activity and

muscular hypotonia are almost constant findings Muscle pains are complained of and weakness or paralysis of the extremities occurs occasionally In one patient observed by the writers presenting a typical picture of acrodynia paralysis of the extremities occurred and persisted for three weeks with thereafter a gradual return to normal function throughout this period sensation in the extremities remained intact It is not unusual for the patients to develop tremors of the extremities and even coma and convulsions There were four patients with convulsive episodes in the series of cases from this clinic[8] Evidences of an increased secretory activity become manifest There is excessive lacrimation and rhinorrhea sialorrhea and profuse perspiration Dehydration usually is evident and is due in addition to the diminished fluid intake to water loss through the skin resulting from the glandular activity

Anorexia vomiting and constipation are among the evidences of gastrointestinal disturbance commonly observed in acrodynia It is not unusual to find by analysis of the gastric contents evidence of achlorhydria There is a normal response of gastric secretion to histamine

Elevation of the basal metabolic rate which has been described in the disease has not been found with any constancy Although the basal metabolic rate may be as high as sixty per cent above normal in many patients dependable determinations of the metabolism have shown a normal or even reduced energy consumption The difficulty in establishing basal conditions for the determination of the metabolic rate is obvious in children who are fretful irritable and suffering from constant pain The blood sugar frequently is abnormally high and glucose tolerance tests may show curves of the blood sugar simulating in some respects those found in patients with diabetes

The urine of patients in the more severe stages of acrodynia has been usually quite concentrated probably due to the partial dehydration of the patient Albumin is found in the urine of almost one fourth of the cases Glycosuria is even more frequent occurring inconstantly in probably a third of the case

Erythrocytosis and leucocytosis are present in the peripheral blood due probably to the partial dehydration mentioned above An elevation of the serum protein has been found to be present in some cases and absent in others In one instance the serum protein was reduced to 4 5 gms per cent although the child had a polycythemia and other evidence of mild dehydration The failure of the serum protein to be elevated in this and similar cases has been thought to be due to the prolonged partial starvation of the patient with considerable destruction of tissue proteins and ultimate reduction in the serum protein The inorganic elements of the blood of patients suffering from acrodynia have been depicted as within normal limits with the exception of the blood calcium which has been reported to be elevated Confirmation of this deviation from the normal of the blood calcium is lacking

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muscular hypotonia are almost constant findings Muscle pains are complained of and weakness or paralysis of the extremities occurs occasionally In one patient observed by the writers presenting a typical picture of acrodynia paralysis of the extremities occurred and persisted for three weeks with thereafter a gradual return to normal function throughout this period sensation in the extremities remained intact It is not unusual for the patients to develop tremors of the extremities and even coma and convulsions There were four patients with convulsive episodes in the series of cases from this clinic[8] Evidences of an increased secretory activity become manifest There is excessive lacrimation and rhinorrhea sialorrhea and profuse perspiration Dehydration usually is evident and is due in addition to the diminished fluid intake to water loss through the skin resulting from the glandular activity

Anorexia vomiting and constipation are among the evidences of gastrointestinal disturbance commonly observed in acrodynia It is not unusual to find by analysis of the gastric contents evidence of achlorhydria There is a normal response of gastric secretion to histamine

Elevation of the basal metabolic rate which has been described in the disease has not been found with any constancy Although the basal metabolic rate may be as high as sixty per cent above normal in many patients dependable determinations of the metabolism have shown a normal or even reduced energy consumption The difficulty in establishing basal conditions for the determination of the metabolic rate is obvious in children who are fretful irritable and suffering from constant pain The blood sugar frequently is abnormally high and glucose tolerance tests may show curves of the blood sugar simulating in some respects those found in patients with diabetes

The urine of patients in the more severe stages of acrodynia has been usually quite concentrated probably due to the partial dehydration of the patient Albumin is found in the urine of almost one fourth of the cases Glycosuria is even more frequent occurring inconstantly in probably a third of the cases

Erythrocytosis and leucocytosis are present in the peripheral blood due probably to the partial dehydration mentioned above An elevation of the serum protein has been found to be present in some cases and absent in others In one instance the serum protein was reduced to 4 5 gms per cent although the child had a polycythemia and other evidence of mild dehydration The failure of the serum protein to be elevated in this and similar cases has been thought to be due to the prolonged partial starvation of the patient with considerable destruction of tissue proteins and ultimate reduction in the serum protein The inorganic elements of the blood of patient suffering from acrodynia have been depicted as within normal limits with the exception of the blood calcium which has been reported to be elevated Confirmation of this deviation from the normal of the blood calcium is lacking

Symptoms

The onset of acrodynia is insidious Frequently the mother cannot state accurately when the disease began although in some instances an upper respiratory infection either initiates the symptoms or quickly becomes an associated process The infant or young child gradually becomes irritable, fretful and sleepless, and refuses food Cessation of growth and progressive loss of weight ensue Profuse sweating, lacrimation and photophobia with excessive secretions from the nose and throat develop The cheeks are bluish red in color with the tip of the nose in many cases, very red The expression of the suffering patient is worried and unhappy Ulcerations of the mucous membranes of the mouth are of frequent occurrence Sooner or later hyperemia alternating with ischemia appears on the hands and feet The palms and soles develop a dull beefy red frost bitten appearance and although the infants show evidence of marked discomfort and older children complain of intense burning and itching in these locations the extremities usually feel cold and clammy Maceration of the skin of the palms and soles occurs followed by desquamation and frequently secondary infection Rashes of the papular type, which itch intensely may appear over the whole body There is a wide variation in the intensity or severity of the cutaneous lesions and it seems quite possible that a patient may suffer from acrodynia and present minimal skin lesions

The patient tends to assume abnormal positions in bed, frequently placing himself in the knee chest position with his head burrowed in the pillows This position has been attributed to the photophobia but as older children with the disease often complain of abdominal cramps we are inclined to believe that even infants may assume this position in an attempt to relieve abdominal discomfort

Except as the result of secondary infection the temperature in acrodynia is not elevated

Physical examination reveals fundamental circulatory disturbances even in early cases often before the appearance on the hands and feet of the typical vascular changes Signs of the circulatory involvement are tachycardia and an elevation of the blood pressure The pulse rate varies usually between 140 and 200 per minute and is little influenced by cry effort or sleep The rhythm is regular The electrocardiogram shows no abnormality except the tachycardia Hypertension is present to some degree in all cases and is said by Feer to be the most constant sign of the disease

In addition to the features mentioned above symptoms referable to the central nervous system with profound mental disturbances frequently appear early and persist throughout the course of the disease Lassitude, apathy irritability and disturbances of the sleep rhythm together with diminished activity and

IV Secondary involvement
- Maceration of skin due to profuse sweating
- Secondary infection
- Dehydration due to excessive water loss
  - Elevated red cell count
  - Elevated serum protein
  - Concentrated urine
  - Constipation
- Loss of weight
  - Negative nitrogen balance

In table II are listed the outstanding symptoms and signs of acrodynia, compiled from the literature and confirmed by the analysis of our series of cases The features of the disease are shown in relation to the known action of various portions of the nervous system Many of the symptoms and signs suggest definitely a cerebral involvement and others point to a spinal cord or peripheral nerve injury Numerically however the manifestations are predominatingly those of a disorder of the autonomic system

Clinical pathological data supporting the conception of a central nervous system involvement are found in examination of the spinal fluid Early in the course of the disease the spinal fluid may show an increase in globulin and a pleocytosis Spinal fluid examinations were made on one or more occasions in seventeen of the patients from this clinic None of these examinations was made at the onset of the disease inasmuch as hospitalization of the patients was not carried out until the process had become quite advanced The analyses showed the spinal fluid to be under normal pressure and to be clear and colorless The cell counts were within normal limits The globulin was increased as determined by the Pandy test in six of the seventeen cases and quantitative determination of the total protein yielded values as high as 250 mgm per 100 c c of spinal fluid The sugar was normal in nine cases and appeared to be abnormally high in the remaining eight cases These findings in the spinal fluid would not indicate the presence in the brain of hemorrhage or gross inflammation The increase in the total proteins however might well indicate a mild inflammatory or degenerative process

Diagnosis

It has been pointed out that acrodynia is characterized by painful red hands and feet peeling prostration paresthesia perspiration and photophobia If to these evidences are added hypertension and tachycardia the diagnosis should not be difficult As in any recently described disease, the typical severe example has become readily recognized but only in the light of accumulated observation and experience are the variations in the clinical picture and particularly

The Kahn and Wassermann reactions are negative in acrodynia Blood cultures are sterile Bacteriologic examinations of the nose and throat yield varied types of organisms such as are found in routine cultures

Roentgenograms of the long bones may show lines of interruption of growth such as appear in children after any long debilitating illness [5] Occasionally, in the later stages of the disease, a generalized osteoporosis is evident

A study of the clinical features of the disease, and the laboratory data make it apparent that there is present in acrodynia a widespread and fundamental derangement involving many organs and tissues of the body Although the pathologic findings are meagre and inadequate to account for the extensive clinical features it does not seem unreasonable, whatever the precipitating cause, to relate the outstanding features of the disease to a disturbance of the central nervous system together with a dysfunction of the autonomic nervous system, as suggested first by Feer

TABLE II

Pathogenesis of the Symptoms and Signs of Acrodynia

I Symptoms of cerebral or spinal involvement
- Apathy
- Muscular weakness and paralysis
- Deep muscle pains

II Symptoms probably cerebral or spinal but possibly due to autonomic involvement
- Hypomotility and hypotonia
- Hyperesthesia
- Coma and convulsions

III Autonomic involvement
- Sympathetic disturbances (overactivity)
  - Vasomotor disturbance (hands and feet less marked on trunk)
  - Dilatation of the pupil and photophobia
  - Tachycardia
  - Sweating
  - Falling of the hair
  - Hypertension
  - Elevated blood sugar glycosuria
- Autonomic disturbances not definitely assignable to sympathetic involvement and possibly due to parasympathetic involvement
  - Salivation
  - Rhinorrhea
  - Vomiting
  - Abdominal pain
  - Hypomotility alternating with colicky hypermotility f gastro intestinal tract
  - Constipation
  - Difficult micturition

medications Tonsillectomy adenoidectomy and sinus operations have their proponents[12] as surgical procedures directed towards relief of foci of infection Because of the tendency to ulcerative and sloughing lesions in the mouth caution might well be exercised toward surgical intervention of this type[9] Autogenous vaccines have been used likewise in an effort to suppres the infection thought to underlie the pathogenesis of the di case[79]

To control the sweating atropine has been used to alleviate sympathetic over timulation ergotamine tartrate has been tried without satisfactory results Inasmuch as none of the measures suggested in the treatment of acrodynia has been efficacious practical therapy at present must consist of treatment directed towards relief of symptoms or prevention of complications The maintenance of cleanliness of the nasal and buccal cavities by soothing irrigations and gargles gives relief as well as aiding to prevent serious local infections Sedatives are frequently required for control of such nervous symptoms as insomnia excitability and extreme discomfort Barbital derivatives seem better adapted to the necessarily prolonged administration than do opium derivatives For the local cutaneous pain or itching calamine lotion hot packs to the extremities or ultraviolet *radiation may give relief Occasionally cold applica*tions to the hands and feet are greatly appreciated

Perhaps the most important feature to be observed closely is the nutrition of the patient Certainly the one positive indication in this prolonged debilitating disease from which recovery is the rule is to prevent severe malnutrition Children may have to be urged to eat yet frequently tolerate a simple complete and well balanced diet quite well without development of any evidence of faulty digestion To avoid the dangers of prolonged inanition it is sometimes necessary to resort to gavage for short periods of time

Recovery from the disease although usually complete is slow and efforts should not be made to urge the child to over activity mentally or physically throughout the long period of convalescence

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4 BILDERBACK J B A group of cases of unknown etiology and diagnosi Northwest Med 1920 XIX 263

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the mild and borderline cases, clearly defined The cutaneous manifestations are less constant than are the circulatory signs of tachycardia and hypertension

Pellagra should be readily distinguished from acrodynia, as should also erythemas due to cold or drugs, on the basis of the lack in these conditions of the constitutional reactions characteristic of acrodynia

Prognosis

The duration of the symptoms is prolonged, several weeks elapse between the onset of the disease and the development of the complete picture The patient then remains weeks or months in an unchanged state which gradually gives way to improvement There exist, however, the widest differences in duration and severity of the illness In certain instances the onset is sudden, and the evolution of the lesions very rapid in a few weeks the symptoms subside and the illness is terminated However, in the majority of cases the disease persists for several months

Periods of exacerbation or recession of severity of symptoms are commonly observed Recurrences have been observed with intervals of two or three months of normal health, but true second attacks of the disease have not been described

The termination of the disease is usually favorable with a slow and gradual return of the child to normal health The nervous symptoms frequently subside first evidenced by improvement in the mental state and the return of muscle tone, the anorexia diminishes, and the child begins to gain weight. The cutaneous and circulatory manifestations may persist for a longer time

Death is due occasionally to manition but most frequently to secondary or terminal infections The fatality rate has varied widely, ranging from five to thirty per cent in different series of cases

Treatment

Ignorance of the true nature of acrodynia prohibits the development of a specific therapy Many forms of treatment have been suggested, but their efficacy is difficult to determine in a disease of variable length, variable severity and good outlook

Good results in hastening the return of the patient to normal health have been claimed for a diet high in vitamins, especially vitamin B The use of endocrine preparations thymus [6] thyroid [7] or suprarenal, has also been subjected to trial The hypothesis suggesting the disease to be of an infectious nature has led to therapy directed towards the healing of infection or the eradication of chronic foci Quinine hexamethylenamine salicylates have been tried as

medications[9] Tonsillectomy, adenoidectomy and sinus operations have their proponents[12] as surgical procedures directed towards relief of foci of infection Because of the tendency to ulcerative and sloughing lesions in the mouth, caution might well be exercised toward surgical intervention of this type[9] Autogenous vaccines have been used likewise in an effort to suppress the infection thought to underlie the pathogenesis of the disease[30]

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CHAPTER XII

BERIBERI AND EPIDEMIC DROPSY

By EDWARD B. VEDDER

Table of Contents

PART I

Beriberi

PART II

Infantile Beriberi

complicated deficiency not only of thiamin but of most of the other vitamins of the B complex as well as vitamins A and E

Geographical Distribution

Beriberi is constantly present or endemic in all those countries where rice is used as the staple article of diet Thus it is very common in all of Eastern and Southern Asia and adjacent islands It is a serious cause of disability and death in Japan China the Malay peninsula the East Indies and the Philippines In China and India beriberi is common in the south rare or unknown in the north where whole wheat millet and other grains are used in place of rice Beriberi has been reported from practically all parts of the east and west coasts of Africa where it is practically constantly present and is particularly prevalent among contract laborers In South America the disease is commonest in Brazil where often it has attained alarming proportions It has occurred also in Venezuela Panama and the West Indies Small outbreaks and sporadic cases have occurred nearly everywhere including England and various parts of Europe the United States and Canada In these countries beriberi is more apt to occur in prisons insane asylums and other institutions Like scurvy beriberi has had a remarkable tendency to occur in ships When the crew is composed of Orientals the beriberi is caused by the too exclusive use of rice and the clinical picture is similar to the beriberi seen in the Orient However European sailors are by no means exempt and beriberi formerly was unusually common on Swedish and Norwegian vessels In these ships the wet form of the disease predominated sometimes complicated by scurvy In recent years as the dietary origin of beriberi has been recognized sporadic outbreaks and ship beriberi have practically disappeared Beriberi was the most common disease in Japanese prison camps in World War II

Epidemiology

Beriberi may occur in any race but because of racial food habits its incidence is high in certain races low in others Europeans in the Orient do not develop beriberi although surrounded by natives having the disease That this immunity is not due to lack of susceptibility is shown by the fact that European sailors and inmates of prison camps and asylums where the diet has been one sided and monotonous often develop beriberi A striking case was the outbreak among the British soldiers in Mesopotamia reported by Hehir

Beriberi may occur at all ages and in both sexes though commoner in men Infantile beriberi of breast fed babies is a frequent cause of mortality in Japan the Philippines and possibly in other oriental countries Among women beri

PART III

Ship Beriberi

PART IV

Epidemic Dropsy

PART V

Beriberi and Malnutrition

PART I

BERIBERI

Synonyms — Polyneuritis endemica kakke (Japanese) barbiers (French) lœmpœ (Java) maladie des sucreries (French Antilles), inchacao or perneiras (Brazil) hinchazon (Cuba), etc

Definition — Beriberi is a deficiency disease usually produced by the too exclusive use of decorticated or polished rice white wheat flour and certain other carbohydrate staples

Clinically beriberi is characterized by degenerative changes in the nervous system including a multiple peripheral neuritis, which may exist alone (dry beriberi) but often is combined with generalized edema and serous effusions (wet beriberi) and by a tendency to cardiac failure and sudden death Wet beriberi and the cardiac symptoms are caused directly by the deficiency of thiamin and may be cured by intravenous injections of thiamin chloride Dry beriberi is a

that Rogers described the serous effusions and in 1812 Marshall described two diseases giving the name barbiers to the dry form previously known as beriberi and reserving the term beriberi for those cases in which edema and cardiac symptoms predominated This classification was followed by le Roy de Meri court and other writers but in 1835 Malcolmson noted that cases that commenced as wet beriberi after a sudden diuresis became transformed to barbiers or dry beriberi and that dry cases often developed edema and con cluded that these were but two types of the same disease This view has since been universally accepted Recent work on edemas of dietary origin indicate that deficient protein intake leads to a low protein concentration in the blood and that when the osmotic tension of the blood is thereby sufficiently lowered edema will occur Some of the disease conditions in which edema is a prominent feature and that have been confused with beriberi may therefore actually be due to a diet deficient in protein Americans in Japanese prisons lost much of their edema when protein was added to their diet Nevertheless Chamberlain and Vedder found in 1912 that the edema of wet beriberi became rapidly dissipated after the administration of a protein free extract of rice polishings and this result has been confirmed many times since We must therefore accept the fact that wet beriberi is not caused solely by dietary deficiency in protein even though this factor may sometimes coexist As will be seen wet beriberi is pure thiamin deficiency and can be relieved promptly by intravenous injections of thiamin chloride

Dry beriberi is a very complicated deficiency Aykroyd and co-workers stated in 1940 that animal experiments and human experiments and the ob servation of the incidence of deficiency diseases show that typical rice diets are deficient in vitamin A calcium and various members of the B_2 complex

In 1943 Vedder tested the B_2 deficiencies of rice by feeding rats on polished rice To this basic diet vitamins A and E and a salt mixture were added The synthetic B factors shown to be necessary were added starting with thiamin and followed by pyridoxin (B_6) riboflavin calcium pantothenate 20 milligrams of choline chloride para aminobenzoic acid and inositol Even with this extensive addition growth was inadequate in the 50 rats used because all of the B factors were not included Synthetic biotin was not then available Yeast powder which contains all the B vitamins will promote growth under these circumstances

While the elucidation of the etiology of beriberi has resulted chiefly from the work of the last thirty years the literature particularly that pertaining to vitamin research is so voluminous that it is impossible even to summarize it In addition while dietary deficiency is accepted very generally as the cause of beriberi there are a few who still favor infection or toxemia as the true cause

Infection —With the development of the science of bacteriology and the identification of the organisms of many infectious diseases a belief arose that

beri is more frequent during the childbearing period, often developing during pregnancy or the subsequent lactation. Among men there is some evidence that hard muscular labor favors the development of the disease. From two to fifteen years of age the disease is relatively rare.

With regard to economic status beriberi is confined chiefly to the poor, the coolies and contract laborers, although the well-to-do are affected often enough to lead some observers to question the dietary origin of the disease. But the ability to procure a good diet does not guarantee that it will be eaten. There are many dietary fads and fancies. In 1925 Kepler reported a case of beriberi occurring in the United States in which the diet was restricted voluntarily to raw starch, and in 1934 Riesman and Davidson reported another case following voluntary drastic restriction of food for an alleged stomach complaint. Oriental soldiers and sailors always have been especially liable to beriberi because rice is the chief component in their rations. In some of the Japanese prisons the prisoners escaped the disease while the guards suffered severely. It was found that the prisoners were rationed on a mixture of barley and rice, while the guards, who bought their own food, ate rice alone.

Beriberi has a marked seasonal variation. In Japan the disease is most frequent and severe from May to September, in the Philippines the greatest incidence is from September to January. Since it has been shown that beriberi may occur in the hottest or the coldest countries, from the equator to Labrador or to the north of Japan, in wet or dry climates and at all altitudes, climate alone can have little influence on the development of the disease. It is probable that seasonal variations in the incidence are due to corresponding changes in the food supply which depends upon the appearance and exhaustion of the harvest at certain regular seasons. This applies not only to grain but also to vegetables and other protective foods, which are cheap and readily procurable at certain seasons, dear and scarce or non existent for the poor at least at other times.

Overcrowding sometimes has been suggested as influencing the development of beriberi and as favoring infection as a cause. But when undermilled rice has been substituted for the polished rice, beriberi has disappeared, although the overcrowding was not corrected and in certain institutions may have been actually increased.

History and Etiology

Beriberi appears to have been recognized in Chinese literature as early as 2697 B.C., but European knowledge dates from Bontius, who clearly described the atrophic form now known as dry beriberi in 1642. It was not until 1808

disease should be reduced to the simplest form possible This principle was stated by Newton in his Principia as the first of four Rules of Reasoning in Philosophy We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances

The evidence that beriberi is caused by the deficiencies of a polished rice diet may be summarized as follows under Epidemiological Observations

Epidemiological Observations

Observations widely separated in time and place have established the fact that beriberi appears when decorticated rice is used as the main staple of diet and that these outbreaks of beriberi disappear when whole or undermilled rice is substituted Standard animal tests have now shown that polished rice has a vitamin B index of approximately 1 6 as compared with 20 for the whole rice and 84 for the rice polishings while the various legumes vary from 20 to 40 Such quantitative information is comparatively recent and the older epidemiological observations still are of historic interest in that they proved that there was something in the external layers of the grain that prevented beriberi

Vordermann analyzed the statistics with regard to the diet of 279 623 prisoners in Java and found that in 51 prisons in which decorticated rice was eaten beriberi developed in the proportion of one case to each 39 prisoners that in 37 prisons using undermilled rice as the staple food beriberi occurred only in the proportion of one case to each 10 000 prisoners Undermilled rice then was adopted and beriberi was eliminated from these prisons

In the Malay States Braddon pointed out that beriberi was unknown among the Tamils who ate only cured rice although very common among the Chinese who used the ordinary white decorticated rice Cured rice is parboiled before husking as a result of which not only is the husk more readily removed leaving the external layers of the grain intact but the process of cooking undoubtedly distributed the vitamin in these layers to some extent through the grain

In Siam Highet showed that beriberi was unknown until milled white rice was furnished Beriberi appeared in epidemic proportions when this rice was introduced but when hand milled or undermilled rice was substituted in the supply of jails schools and other institutions under government control beriberi disappeared from these institutions

Beriberi was a serious cause of disability among the Philippine Scouts from 1902 to 1910 This body of native troops approximately 5 000 strong were supplied with the finest polished rice that could be purchased and during this time often had as many as 500 cases of beriberi annually The issue of decorticated rice was prohibited in 1910 The incidence of beriberi declined abruptly and as the use of the undermilled rice became really effective beriberi was

beriberi was infectious and many attempts were made to isolate the causative organism from the blood and stools of patients The early methods used often were very crude and later investigations with improved technique have shown that the blood is sterile Moreover, the different investigators all found different organisms and while some of these were toxic when injected none of them produced beriberi in animals In no case has any proof been afforded that the incriminated organisms really caused beriberi Yet the theory of infection dies hard As late as 1929 thirteen Japanese investigators sponsored a beriberi bacillus, which was identical with *B coli communior* in culture, but which they claimed agglutinated and gave complement fixation reactions with the blood of beriberi patients This finding has not been confirmed and is not accepted by the majority of Japanese workers In Brazil the belief is very general that beriberi is of infectious origin, chiefly because it is believed that beriberi occurs frequently among those consuming an adequate diet It is noteworthy that no matter how deficient a diet may be, the authorities who prescribe it, or the people who habitually consume it, will quite honestly state their belief that it is adequate Such statements from Brazil fail to carry conviction especially when it is known that two of their staples of diet are rice and farinha and that beriberi has developed in the Brazilian navy when rationed on these staples

Intoxication —Other observers have thought that beriberi is due to an intoxication either caused by some deterioration of the food consumed or by auto-intoxication These theories are suggested largely by the clinical resemblance of beriberi to certain well known forms of toxic peripheral neuritis Braddon advocated the theory that decorticated rice became toxic owing to the growth of some hypothetical organism and that parboiled or whole rice was protected from the action of this germ by the external layers of the grain Hamilton Wright believed that the symptoms of beriberi were produced by a powerful toxin secreted by an organism multiplying in the duodenum These views are only of historical interest All efforts to extract a toxin from rice or other foods that would produce beriberi have failed, nor has it ever been shown that the blood of patients suffering from beriberi or of fowls suffering from polyneuritis gallinarum is toxic However, certain investigators still hold that as the result of the dietary deficiency which is admitted auto-intoxication develops as the result of faulty metabolism and that the toxin so produced causes degeneration of the nervous system and the other lesions of beriberi McCarrison subscribed to this theory as late as 1928 While I gladly admit the great value of his contributions this particular view must be rejected by me first as not proven and second as demanding a hypothetical toxin to explain results that can as well be explained as a simple inability of the tissues to grow and function in the absence of the essential vitamins Scientific explanations of

were eating the cured rice The conditions were then reversed and the group that previously received cured rice was supplied with decorticated rice Again after about three months beriberi appeared in this group while the workers who had previously developed beriberi as the result of eating decorticated rice improved and no fresh cases appeared in this group after the diet was changed to cured rice This experiment was well controlled and the workers mingled freely during the day, so that the appearance of beriberi in restricted groups cannot be attributed to infection The disease always followed the use of de corticated rice and did not appear when cured rice was used

A somewhat similar experiment with similar results was subsequently per formed by Strong and Crowell in Bilibid prison Manila In this experiment the men were completely isolated in stone cells and it was shown that beriberi was produced by the use of decorticated rice

Animal Experiments

In the year 1897 Eijkman found that fowl fed exclusively on decorticated rice developed a paralytic condition closely resembling dry beriberi The disease was called polyneuritis gallinarum and subsequently it was found that pigeons and other birds are similarly susceptible Eijkman also found that fowls fed exclusively on whole rice or on decorticated rice plus the polishings removed in the milling process were protected This work by providing an experimental animal opened the way for a long series of investigations and it is gratifying to know that Eijkman finally received a Nobel prize for this con tribution

At first it was thought that decorticated rice was toxic and that the addition of the rice polishings neutralized this toxin But Fraser and Stanton extracted decorticated rice with alcohol and showed that the extracts so obtained were not toxic but that on the other hand when fowls were fed on an exclusive diet of decorticated rice the development of polyneuritis was prevented by an al coholic extract of the whole rice or of the polishings removed from the rice in the milling process It became evident therefore that the rice polishings contained some substance that protected fowls fed on decorticated rice from the development of polyneuritis and attempts were made by a number of independ ent observers to identify this substance It was found that the protective substance could be extracted from rice polishings by water and to a less extent by alcohol but not by ether that it was dialyzable that it was destroyed in its extracts by heating to 120 C that it was absorbed from its extracts by animal charcoal and by kaolin and that it could be precipitated completely by phosphotungstic acid

These characteristics indicated that the protective substance was an organic

completely eradicated Undermilled rice has been furnished continuously since 1910, and for the past 25 years beriberi has never been a cause of admission to sick report and this in spite of the fact that these soldiers live in a country where the disease is present constantly A similar improvement was made at about the same time in all civil governmental institutions in the Philippines when undermilled rice was introduced by executive order on the recommendation of Victor G Heiser then Director of Health

It was also found that beriberi could be prevented by the addition of other foods to a ration consisting largely of decorticated, beriberi producing rice Takaki succeeded in practically eliminating beriberi from the Japanese navy by the introduction of a new ration in which the chief improvement was the addition of an increased amount of legumes and a considerable increase in other vegetables Saneyoshi stated that in the Japanese army from 1882–1884 from 18 to 26 per cent of the soldiers developed beriberi Barley was added to the ration and the number of cases of beriberi fell to below one per cent of the command Barley will also prevent the development of polyneuritis in fowls fed on decorticated rice Grijns found in 1901 that polyneuritis gallinarum could be prevented by the addition of a legume (*Phaseolus radiatus*) to a diet of decorticated rice, and Hulshoff Pol found that this legume, known locally as katjang idjoe would also prevent the development of beriberi among men fed on decorticated rice These epidemiological observations, particularly those of Braddon which were very comprehensive although they have been referred to so briefly, suggested certain feeding experiments on human beings which confirmed and extended this epidemiological evidence

Human Feeding Experiments

Fletcher s experiment at the Kuala Lumpur insane asylum was as follows On December 5 1905 all the lunatics were numbered The odd numbers were sent to the East ward and were supplied with decorticated rice The even numbers were sent to the West ward and supplied cured rice (whole rice) The experiment was continued two years Excluding patients who were in the asylum less than twenty eight days and those who had beriberi on admission the results were as follows 154 patients were fed on cured rice, and none of these developed beriberi, 153 patients were fed on decorticated rice of whom 65 or 42 5 per cent developed beriberi in the asylum

Fraser and Stanton took 300 Javanese laborers into a virgin jungle, where they were employed and divided them into two groups The first group was supplied with decorticated rice and the second group was supplied with cured rice (whole rice) In three months beriberi commenced to appear among the laborers eating decorticated rice but did not appear among the laborers who

Function of Thiamin

Cowgill published a formula for the daily requirement of thiamin (Vitamin B) His formula was $\frac{\text{Vitamin}}{\text{Calorie}} = 0.0000284$ Weight in grams This is actually a vitamin B calorie ratio for any particular weight Knowing the vitamin B index of all ordinary foods it is possible to determine the total amount of thiamin in a given ration as compared with the total calories consumed and to compare this with the weight of the individual

Investigating diets upon which beriberi is known to have developed Cowgill found that in general the thiamin ratio fell considerably below the weights of the individuals concerned R R Williams on the other hand believes that the vitamin calorie ratio required for a given species appears independent of the weight of the individual within the limits of experimental error

Thiamin possibly in a free state more certainly in the form of its pyrophosphate serves in the enzymatic disposal of pyruvic acid formed in normal carbohydrate metabolism This action is accompanied by an increase in carbon dioxide and an increased utilization of oxygen Certainly one of the undoubted results of thiamin deficiency is the accumulation of pyruvic acid in the blood The co-enzyme function of thiamin pyrophosphate thus is established Decreased carbohydrate intake has been shown to delay the onset of polyneuritis in animals and abundant carbohydrate increases the thiamin requirement The substitution of fat for carbohydrate lessens the thiamin requirement and delays or prevents the development of polyneuritis especially if there is an adequate choline supply

However in spite of these demonstrated facts the accumulation of pyruvic acid in the blood has failed experimentally to produce any of the symptoms of beriberi in animals and it must be postulated that other cellular damage must be produced by the deficiency of thiamin There is more to be learned concerning the physiological action of thiamin and the method of producing the cardiac changes and the development of anasarca which are directly caused by this deficiency

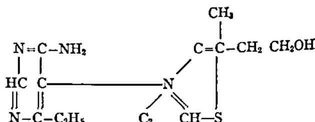
PATHOLOGY

When the patient has died suddenly from acute beriberi the body often is apparently well nourished and cadaveric rigidity is well marked There is usually some edema particularly of the legs since sudden death is most frequent in the wet cases The blood remains fluid a long time and on making the first incision there is often a profuse flow of dark-colored blood and the tissues are seen to be edematous In those dying of the chronic and atrophic

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In the meantime Stepp in 1909 and McCollum about 1912 were demonstrating that animal fats also contained an accessory food factor necessary to life McCollum designated it fat soluble A and a little later named a second accessory factor water soluble B This initiated the alphabetical designation of the vitamins and both A and B subsequently were found to consist of several vitamins which received new letters To follow this investigation would take us much too far afield and it is only necessary to state here that the vitamin classified as B by Americans and B_1 by English investigators is the antineuritic vitamin found in rice polishings yeast and legumes in considerable amount

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Williams and Cline completed the synthesis in 1936 and marked it thiamin It is now readily available

Evidence of the etiological role of this vitamin has been obtained in Manila by Hermano and others through feeding pure crystallized vitamin furnished by Williams to cases of human beriberi

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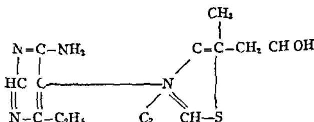
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ponding to these changes but it seems certain that although the symptoms of beriberi have been attributed in the past chiefly to the peripheral neuritis the condition is not a simple polyneuritis but is a degeneration of the entire nervous system as well as of other organs

Muscles —The changes in the muscular system are most probably the result of nerve degeneration but a primary fault of metabolism due to the dietary deficiency cannot be entirely excluded The muscles are much wasted and may be dry and pale Microscopically there is a diffuse parenchymatous degeneration combined at times with fatty and hyaline degeneration

Heart —The heart is practically always hypertrophied and this usually is combined with dilatation death being caused most often by this inadequacy of the heart This change is most marked on the right side and frequently affects only that side In 125 necropsies on cases of beriberi Ellis found the average weight of the heart to be 15 37 ounces (427 8 grams) while over the same period of time the hearts of 04 patients who died of other diseases averaged just under 9 ounces (288 grams) the latter being a normal weight for Asiatics The right side of the heart was much enlarged in nearly every case of beriberi

On microscopic examination the myocardium may show fragmentation of the muscle fibres with some hyaline and fatty degeneration Foci may be found where the muscle fibres have been replaced by fibrous tissue and the bundle of His has been shown to be implicated in certain cases A hypertrophied heart should be a strong heart whereas death is almost invariably caused by the failure of the right heart Aalsmeer and Wenckebach concluded that the hypertrophy is not caused by any increase in the number or functional size of the muscle fibres but that the increased size and concomitant weakness is caused by the imbibition of fluid by the muscle fibres and that when the proper diet is administered the heart returns to its normal dimensions melting away like snow in the sun

Weiss and Wilkins stated the myocardium of the beriberi heart showed hydropic degeneration of the muscle and conducting fibers and an increase in the intercellular substances but unaltered water content In the electrocardiogram they found changes in the T waves and prolongation of the electrical systole (Q–T)

Weiss and Wilkins measured the circulation in 13 cases The most significant finding was that patients with enlarged heart rapid heart rate gallop rhythm dyspnea generalized edema low vital capacity and elevated venous pressure had a normal or increased velocity flow and a low arterio-venous oxygen difference This differs from other types of organic heart disease in which generally there exists a direct relationship between the degree of congestive failure and the slowing of the blood flow This increased capillary pres ure naturally leads to generalized edema The rapid blood flow returns the blood to the right side of

form of beriberi the muscles especially of the legs and often the arms are wasted, rigidity is not marked, and edema usually is absent The changes characteristic of beriberi may be described in the following order

Few gross changes can be detected, but nevertheless the entire nervous system is profoundly altered as may be demonstrated by microscopic examination with appropriate staining methods

Peripheral Nerves —The changes in the peripheral nerves vary from a slight medullary degeneration of a few fibres in some cases to almost complete degeneration of the nerve in other cases In these latter cases generally of the dry type there is complete degeneration of both sheath and axis cylinder of the majority of the fibres The axis cylinder is fragmented and is only to be found near Ranvier's nodes, while only vestiges of the medullary sheath remain The intensity of the degeneration and the proportion of fibres affected may vary in different nerves in the same case, but all peripheral nerves commonly show some degeneration Usually it will be found most advanced in the sciatic nerve the legs being the first and most seriously affected limbs A branch of the sciatic and a piece of the pneumogastric may be selected as a routine Degenerative changes have been found also in fibres of the sympathetic system

Spinal Cord —The membranes often are congested and edematous and the cord itself may appear softer than normal On microscopic examination it will be found that scattered fibres in all tracts show the same degenerative changes seen in the peripheral nerves in varying degrees of intensity

The cells also, both from the anterior horn and from the posterior spinal ganglia show degenerative changes indicated by chromatolysis of the cellular material The tigroid substance which normally appears throughout the cell as a skein or network when stained by Nissl or Giemsa stains, remains only as a faintly staining granular material grouped at one end of the cell, while the remainder of the cell is clear and unstained Similar changes have been described in the nerve cells of pigeons that have been exhausted by long flights In other cells in addition to this change the nuclei may be swollen, dislocated and fail to stain as deeply as they should Such changes have been well described by Hamilton Wright and Bentley found the changes in the cord so striking that he regarded beriberi primarily as a cord disease Identical changes were found in the cords of fowls suffering from polyneuritis gallinarum by Vedder and Clark and similar degenerative changes have been found in the sympathetic ganglia both in beriberi and polyneuritis gallinarum

Brain —Lhermite has found marked lesions in the brain in beriberi indicated by a progressive disintegration of the cells associated with proliferation of neuroglia Funk found marked chemical changes in the brains of fowls suffering from polyneuritis gallinarum There are no mental symptoms corres-

Symptomatology

Depletion Period

When a diet deficient in thiamin is adopted physical impairment begins as soon as the reserve stock is depleted We do not know how much thiamin man can store Experimental work on birds has shown that they cannot store this vitamin for degenerative changes can be demonstrated in the nerves of fowls fed on decorticated rice for only 7 days

Physical impairment in man may also appear early R D Williams and his collaborators fed human subjects on low thiamin diets and found that the shortest time for clear evidence of this deficiency was 12 days Such early signs of thiamin deficiency easily may be missed under the title of neurasthenia

Jolliffe and his co-workers have also shown that the polyneuritis of chronic alcoholics is due directly to thiamin deficiency and may therefore truly be called beriberi Alcohol is completely devoid of thiamin and the chronic alcoholic does not eat well

It may still be said that when a diet deficient in thiamin is adopted the length of time that will elapse before the definite appearance of beriberi is the depletion period This was definitely established by the various human feeding experiments confirmed by certain epidemiological observations In the experiment of Fraser and Stanton the symptoms of beriberi first appeared among the men receiving decorticated rice after 89 days In Strong and Crowell s experiment the depletion period was somewhat longer On an exclusive rice diet the depletion period can be placed with great exactness at from 3 to 4 months This is the shortest time in which beriberi can be expected to appear in a normal individual

When consuming a diet of rice containing small additions of adhering peri carp or a diet whose staple is decorticated rice but with various additions of meat and vegetables some antineuritic thiamin commonly is supplied Should the amount so supplied be insufficient that is less than the minimum amount which will maintain healthy metabolism the patient will develop beriberi in as severe a form as though the diet consisted of rice alone but only after a more or less prolonged depletion period This fact has been demonstrated conclusively by animal experiments On the other hand beriberi can develop and often has appeared less than 3 months after the introduction of a deficient ration This shortening of the depletion period is due either to the fact that the individuals concerned previously have lived on a partially deficient diet or that they have been subjected to hard physical labor or other metabolic stresses In this con nection it should be noted that the men used by Fraser and Stanton were em ployed in road construction while those used by Strong and Crowell were isolated in cells to avoid the possibility of infection and consequently performed no labor

the heart at an increased rate As the right heart is weaker than normal, it will fail to deliver blood to the lungs as fast as it is received from the venae cavae and congestion of the abdominal viscera commences followed by pulmonary edema Working against this obstruction the right heart fails completely, its chambers dilate, and we have the acute beriberi heart

Edema and Serous Effusions — Anasarca hydropericardium hydrothorax and ascites are found in a number of the cases, the exact proportion depending upon the predominance of the wet type of cases in the locality Anasarca is present in practically all wet cases Hydropericardium may be found in from 50 to 75 per cent of all cases Hydrothorax is less frequent, and ascites still less common Thus in Ellis' series of 125 cases ascites only occurred 5 times hydrothorax 10 times while hydropericardium was found 81 times In another series of cases hydrops of all the serous cavities was found in 20 per cent of the necropsies The effused fluid is clear and of a peculiar greenish yellow color There may be from 100 to 500 c c of this fluid in the pericardium and from 100 to 1 000 c c in the pleural cavity Varying degrees of edema of the lungs may be found in about 80 per cent of cases dying suddenly, and after death froth may be found in the mouth

Adrenals — There has been no sufficient study of the adrenals in beriberi Several observers have found these glands congested McCarrison found that the adrenals of fowls suffering from polyneuritis gallinarum are considerably enlarged and that the secretion of adrenalin by these enlarged glands is proportionately increased An increase in adrenalin might explain the increased capillary pressure which leads to edema

Chronic Passive Congestion of the Abdominal Viscera — Such congestion usually is found in the liver, spleen and kidneys There may be a typical nutmeg liver and the spleen usually is somewhat enlarged and congested The mucosa of the stomach and duodenum often is congested and numerous punctate hemorrhages or ecchymoses into the mucosa of these organs are found frequently This congestion of the duodenum led Hamilton Wright to consider that beriberi is caused by an infectious duodenitis, but this condition is a late manifestation and part of the general congestion of the abdominal viscera caused by the failing right heart In the lungs subpleural ecchymoses are frequent also and are just as typical of beriberi as the duodenitis

Of these pathological findings none alone is diagnostic of beriberi but the combination of nerve lesions enlarged right heart together with anasarca and effusions without nephritis is diagnostic of beriberi There is no other disease that presents this peculiar combination of pathological changes It must however be remembered that anasarca does not occur in dry beriberi The diagnosis of these cases may be made during life, but at post mortem it would be difficult to distinguish them from the various forms of peripheral neuritis

On examination it will be found that the muscles of the legs and especially of the calves are painful when squeezed and here may be some loss of sensation over the distribution of the anterior tibial nerve Slight edema of the feet and legs is common

The patient may remain in this condition for months or years with alternate improvement or exacerbation of symptoms This condition has been described as rudimentary beriberi and is found frequently in mothers whose children repeatedly have died of infantile beriberi On the other hand the patient may die suddenly in an acute cardiac seizure These sudden deaths in patients in whom the disease was not suspected have given rise to the descriptive terms of pernicious or fulminating beriberi More often the patient gradually becomes progressively worse and the symptoms of marked peripheral neuritis appear sometimes combined with rapidly progressing edema and increasing cardiac incapacity

As the disease progresses in this way the muscles become weaker and at the same time acutely sensitive so that the slightest pressure causes pain and the patient is apprehensive whenever the doctor approaches The extensors of the foot usually are affected first followed by the muscles of the calf then the muscles of the thigh In more serious cases the muscles of the arm also atrophy a little later and in the same order the muscles of the forearm going first In the worst case the muscles of the trunk also atrophy and the patient become confined to bed More often he is able to be about after a fashion with the aid of a cane There is no gait that is characteristic of beriberi for the peculiarity depends upon the extent and character of the nervous and muscular involvement Thus in early cases there may be toe drop with a steppage gait Later an ataxic gait develops and Romberg s sign is present Still later there is no gait at all and the patient shuffles about with the aid of a cane or assists him self by holding on to the beds During convalescence the muscles become spastic and the gait frequently resembles that of spastic spinal paralysis It has been noted that fowls that have developed polyneuritis as the result of rice feeding and have been treated with an extract of rice polish develop a similar spastic gait so that it may be assumed that this spasticity is associated in some way with improvement and is a hopeful sign During the course of the illness the muscles give the electrical reactions of degeneration

The muscular reflexes are generally diminished or lost The patellar reflex has been most studied because the atrophy begins first and is most extensive in the leg It is claimed that the patellar reflex may be increased in very early cases but generally when first examined the reflex will be found impaired or completely lost When lost it may remain absent for months after recovery is apparently complete indicating that the damage to the nervous system is repaired very slowly

Types of the Disease

The symptoms of beriberi may be divided logically into three syndromes corresponding to the pathological alterations as follows

1 Symptoms referable to degeneration of the nervous system
2 Symptoms produced by the generalized edema and the serous effusions
3 Symptoms depending on the cardiac hypertrophy and dilatation including the passive congestion of the viscera and the tendency to sudden death

In accordance with this classification the clinical picture presented by any case of beriberi depends upon the proportion in which these three types of symptoms are blended together Cases, in which the symptoms are chiefly dependent upon the degeneration of the nervous system, have been called dry beriberi Cases, in which the tendency to edema and serous effusions is most pronounced, have been called wet beriberi Cases in which the heart is seriously affected early in the disease and in which sudden death often occurred without warning have been called acute pernicious beriberi

Some writers in earlier years thought that the disease here described as beriberi in reality consisted of two diseases, 'barbiers', corresponding to dry beriberi and 'beriberi, corresponding to wet beriberi Malcolmson showed in 1835 not only that these two conditions frequently coexisted, but also that, while the disease might begin as wet beriberi, it frequently terminated as dry beriberi and vice versa Since that time it has been customary to describe dry beriberi and wet beriberi as types of the same disease However, it should not be forgotten that older clinicians regarded these types as distinct diseases especially *in view of the fact that there is considerable experimental* evidence indicating that several vitamins are deficient in the diet that produces dry beriberi

Course of the Disease

The onset generally is insidious For days or weeks the patient is languid readily fatigued and experiences a heaviness of the legs a stiffness of the muscles and increasing indisposition and inability to walk When he does exert himself he may suffer from palpitation and loss of breath after very slight exercise At the same time gastrointestinal disturbances are common and are manifested by loss of appetite and either diarrhea or constipation and discomfort after eating with nausea or even vomiting It may be noted that perhaps the earliest symptom of vitamin B deficiency in both birds and dogs is anorexia In dogs the motility of the stomach is impaired and if fowls are fed by hand the rice remains in the crop and is not passed on to the gizzard Men may lose their appetite, but they think they must eat and the gastrointestinal disturbances probably result from similar inability of the muscular coat to contract

increased fluid in the pericardium Murmurs are common but usually are systolic and functional While there is nothing to prevent a person with a valvular lesion from developing beriberi no valvular lesion is characteristic of that disease The second pulmonic sound often is sharp and accentuated and may be reduplicated This together with the necropsy findings of congestion of the abdominal viscera and pulmonary edema indicates an increased pressure in the pulmonary circulation When this occurs slowly, it may give rise only to a certain amount of cardiac and respiratory embarrassment but when dilatation occurs suddenly it results in agonizing pain, acute dyspnea and sudden death a condition resembling acute cor pulmonale of its usual etiology

There is nothing characteristic of the pulse during the ordinary course of the disease Usually it is small easily compressible and irregular as would be expected in any condition in which the myocardium is weak

In the absence of cardiac accident the patient may linger in the hospital *for weeks or months until gradually the atrophied muscles recover their tone* and strength and the patient walks and performs various exercises with increasing ease During this time almost certainly as the result of some change in diet swollen dropsical cases pass greatly increased quantities of urine The edema subsides rapidly and perhaps then shrunken muscles stand revealed The apparently robust limbs have disguised an extensive muscular wasting and a case of wet beriberi has been transformed into a case of dry beriberi In this manner each case presents its individual variations the symptoms of peripheral neuritis cardiac incompetency and edema being commingled in all proportions and grades of intensity Most patients are only moderately affected are quite able to be about and perhaps only ten per cent of those affected will seek admission to hospital

Aphonia is a peculiar symptom that requires special mention for it occurs with some frequency in chronic adult cases and more often in infantile beriberi The speaking voice is lost and the patient can only whisper This symptom *is attributed to paralysis of the muscles of the larynx following degeneration of* the pneumogastric nerves It was described as early as 1642 by Bontius who said While suffering from this disease the sound of my voice was so feeble for a whole month that those sitting next to me could hardly understand me

Beriberi is not a febrile disease It lasts for months and consequently it is not uncommon for patients to have some fever during the course of the illness Intercurrent infections are probable in the course of any chronic disease and malaria dysentery and tuberculosis are common in the countries where beriberi is endemic and such patients probably are more than usually susceptible to any infection

Blood — There are no characteristic morphological changes A moderate anemia is to be expected but usually neither the red cells nor the hemoglobin

Combined with atrophy and weakness of the muscles are various sensory disturbances usually areas of anesthesia or various paresthesias The distribution of the anesthetic areas depends upon the nerves involved, but like motor disturbances they are more apt to appear first on the lower leg particularly over the anterior surfaces The anesthesia may be complete so that the prick of a pin cannot be felt but often it is partial, and the sharp pin may be felt merely as a slight touch or the sensation may be considerably delayed Such an area of anesthesia around the mouth has been described Perception to heat cold and pain are all diminished in the areas supplied by degenerated sensory nerves The paresthesias consist of sock like disturbance of sensations of heat prickling numbness, formication and itching Such sensations, while not serious, are very annoying

In other cases the atrophy of the muscles is less marked or appears so, being masked by the extensive edema Edema also commonly appears first in the feet and legs and may be confined to these parts, but in many cases it ascends to the thighs and gradually extends over the entire body Associated with the edema there is commonly some hydropericardium and hydrothorax The hydropericardium which is most frequent, is hard to diagnose by physical signs because of the hypertrophy of the heart, which generally is present, and often is not found until after death The amount of fluid in the thorax may be considerable and cause respiratory embarrassment, it may be detected readily by the usual physical signs

Epigastric distress precordial pain, palpitation and dyspnea are concomitant symptoms that at times are very distressing These symptoms may be due partially to accumulations of fluid but are chiefly due to incompetency of the heart muscle Such symptoms may be mild and continuous but are very likely to occur in paroxysms, which come on suddenly and without warning Thus a patient who has not been considered to be seriously ill, and who has caused the physician no anxiety, may after a slight exertion or for no perceptible reason at all be seized with a horrible, boring precordial pain He gasps for breath his face becomes cyanosed and agonized On examination the heart will be found to be palpitating irregularly and violently, while the pulse becomes small and thready and a venous pulse appears in the veins of the neck Death is the frequent result of this sudden dilatation following the weakness of the musculature, and mortality in beriberi is practically all caused by this sudden failure of the heart Such sudden deaths may occur at any stage of the disease but are particularly frequent in the wet type

The heart is almost always hypertrophied particularly on the right side and also may be dilated On examination the apex beat is displaced downward and outward and percussion shows the heart enlarged also to the right This may be confirmed by an x ray which assists in distinguishing hypertrophy from

In such cases an attempt must be made to supply a diet adequate in vitamin content

It should be remembered that beriberi has occurred often together with scurvy particularly in outbreaks occurring on ships

Differential Diagnosis

Individual cases particularly when occurring in a European or American may present considerable difficulty in diagnosis Such cases usually are alcoholic neuritis However it is well known that those who are addicted to alcohol usually *fail to eat a proper diet and it has been suggested that such cases are in reality* suffering from a deficiency of thiamin and treatment with that vitamin has been proposed This has now been used so often successfully that there is no longer doubt that alcoholic neuritis is really a form of beriberi

The diagnosis of beriberi usually is simple among Oriental races who as a rule use little alcohol especially in the presence of a definite outbreak There is *no disease except beriberi that presents at the same time the three symptom* complexes of peripheral neuritis cardiac hypertrophy and weakness and edema with serous effusions In the presence of these syndromes the peripheral neuritis caused by arsenic lead and other intoxicants can be excluded The history of a deficient diet usually can be obtained especially if the clinician is familiar with the articles of diet that are deficient in vitamins and produce beriberi In Ori*entals the fault is almost always the too exclusive use of rice and in jails and* asylums in Europe and America it is the too exclusive use of white bread

True heart disease and nephritis must be excluded also The presence of an unexplained peripheral neuritis naturally suggests beriberi and should lead to investigation of the diet during the past three months There are no cardiac valvular lesions in beriberi *In nephritis albumen and casts are constant* and the blood pressure generally is increased while in beriberi usually it is decreased and abnormal urinary findings are quite exceptional When beriberi has once appeared among soldiers laborers prisoners or other groups of men receiving the same diet examination will show that many others may be found that suffer from weakness of the legs *anesthesias and loss of patellar reflexes* It is among such cases of so-called rudimentary beriberi who perform all their duties and are supposed to be normal that sudden unexpected deaths occur Therefore as soon as the diagnosis of beriberi is made in such a group the responsible medical officer should make a survey of the organization to detect all the cases

Such mild cases may be detected rapidly by a simple examination as follows

1 *Squeeze the muscles of the calf to detect muscular tenderness* Normal muscles will stand much pressure without causing pain while relatively slight pressure may cause pain in those suffering from beriberi

2 Test the anterior surface of the tibia with a pin for anesthesia Men who

are seriously reduced The leucocytes generally are about the normal number but a differential count may show that the polymorphonuclear neutrophils are decreased with a corresponding increase in the lymphocytes This altered differential count is found often in debilitated conditions and without particular significance The same may be said of the moderate shift to the left by the Arneth or Schilling methods

Blood Chemistry —Fleming in 1923 made a study of the blood chemistry of 7 cases of beriberi with edema and 23 cases of beriberi without edema as compared with 8 surgical convalescents in the same hospital All were Filipinos In both groups beriberi and controls the non protein nitrogen, urea nitrogen and creatinin were low as compared with the normals for Americans Uric acid was as high or higher than in Americans, but the beriberi cases averaged lower than the controls The values for blood sugar all fell within the normal range The basal metabolic rate and the respiratory quotients of beriberi patients were normal With the percentages of heat obtained from the combustion of protein, of fat and of carbohydrate, these facts point to a normal utilization of the food eaten These findings serve as an explanation of the fact that some beriberi patients appear to be well nourished The fault of metabolism that is the cause of beriberi cannot be detected by these examinations But that it is a fault of metabolism cannot be doubted

The Urine —The quantity of urine generally is diminished, the specific gravity is low, and the excretion of urea, uric acid and phosphoric acid is below normal but as the excretion of these substances in the urine of Oriental races has been found to be below the standard for the urine of Europeans, these findings are of little significance Albumen and casts may be found in some cases, but as they are not constant and form no part of the clinical picture of beriberi per se it may be concluded that they are present only in those cases in which congestion of the kidneys is marked There is no true nephritis in beriberi, and the edema that occurs is quite independent of kidney changes Fleming found no evidence of damage to the excretory function of the kidney in beriberi, either in patients with edema or in those without this symptom

Complications

Beriberi may be associated with other diseases such as malaria and the various intestinal and pulmonary infections Bronchopneumonia frequently is found at necropsy It is an interesting speculation if the neuritis attributed to malaria dysentery and other infections may not in many instances be caused by mild symptoms of beriberi Certainly neuritis complicating the various infections is seen more commonly in Oriental races than among Europeans Many of these infections also are chronic and are treated with one sided or liquid diets

There is always danger of sudden and unexpected death in any case of beri beri and therefore in the individual case a guarded prognosis may be given and the patient should be warned of the danger of any sudden exertion

In those cases in which the symptoms of peripheral neuritis are marked recovery is apt to be slow and is not to be expected immediately even when a proper diet has been provided The damage to the nervous system is extensive and has progressed for months before the development of the clinical symptoms regeneration of nerve tissues is also slow Convalescence is generally a matter of weeks or months and even when the patient is apparently restored to health the regeneration of the nervous system is not complete The lost reflexes return some time after the patient has been able to walk and transact his affairs

However both fowls and pigeons suffering from polyneuritis have recovered the ability to walk and fly within several hours after treatment with an active preparation of vitamin B even though marked degenerative changes in peripheral nerves have been found months after their apparent recovery From this it may be inferred that most of the symptoms of muscular weakness may be caused by exhaustion of the motor cells rather than nerve degeneration and that except in the most advanced cases of human beriberi with great muscular atrophy a sufficient number of active nerve fibres remain Should this be true we may expect prompt cures in certain cases of beriberi since thiamin is now in common use

Treatment

Since beriberi is caused by a dietary deficiency no drugs have any specific action and their use is purely symptomatic Thiamin is not considered as a drug but as the deficient vitamin

The great danger in beriberi is from sudden heart failure A careful study should be made of each patient and the degree of hypertrophy determined if possible by fluoroscopy and the condition of the heart be determined both by symptomatology and electrocardiography If there is any cardiac disturbance such patients should be kept in bed and not allowed to make any exertion until after treatment This consists in intravenous injections of thiamin chloride in doses of 50 milligrams twice a day Larger amounts have been used safely but it is probable that no more than 50 milligrams can be utilized at one time and larger doses mainly are excreted in the urine This treatment should relieve promptly the cardiac disability and dispel the edema The intravenous use of thiamin then is no longer necessary and further doses can be administered by mouth

Thiamin may relieve also many of the symptoms of dry beriberi including the muscular tenderness Ampoules of thiamin for intravenous use are readily available

have beriberi often have areas in which they cannot feel the pin even though prodded until blood flows

3 Test the patellar reflex Any modification is suspicious but usually in real cases the reflex is diminished in one or both legs

4 Make the patient squat upon his heels after the Oriental manner of sitting If the patient is suffering from beriberi this may cause pain, and there may be inability to arise without using the hands

In 1931 Aalsmeer and Richter described the "adrenalin effect", that is a marked fall in diastolic pressure after the injection of adrenalin in beriberi patients The diastolic pressure is registered, adrenalin is administered in a hypodermic dose of one milligram and the diastolic pressure observed every five minutes thereafter until the effect is obtained It will bring the pressure down to the zero point in a case of beriberi, and there will be an auscultatory murmur that will persist even on complete relaxation of the pressure on the artery as long as the patient is under the influence of adrenalin This adrenalin acts primarily on the heart increasing its output, but it also dilates the peripheral vessels A pulse is, therefore, produced of considerable volume but in which the pulse wave recedes rapidly Aalsmeer has returned to this subject in several publications and claims not only that it is a useful diagnostic point but may even be used to test the effect of various additions to the diet

Prognosis

The mortality in beriberi varies greatly in different outbreaks and localities Mortalities of from 50 to 70 per cent have been reported, but this must be regarded as quite exceptional Hospital statistics also are misleading because only the more serious cases are admitted In such cases the hospital mortality may range between 10 and 20 per cent Statistics compiled from various prisons and military establishments indicate that the average mortality is from 3 to 5 per cent

The variation in mortality in different outbreaks depends upon several factors In general the mortality from the wet type is much higher than from the dry type and the proportion of these types probably depends upon the character of the diet Again if the deficient diet that produced the disease is continued without change the mortality will be high The very high reported mortalities have occurred usually on ships or in other circumstances where no change in the diet was possible In studying infantile beriberi it was by no means unusual to find mothers who had lost five or six infants successively all of whom were breast fed On the other hand, if cases are seen early and the proper diet can be furnished, the mortality is very low Almost all of such cases recover, and if the diet of the group is corrected no more fresh cases develop

If rice be placed in a dish and covered with Gram's iodin solution the starch exposed turns black on contact with the iodin If the rice has been completely decorticated the entire grain becomes black On the other hand in an under milled rice the starch will be protected from this action by the external layers of the grain and the greater part will remain unstained When whole rice is tested the external layers are intact and the starch will not be stained at all With a little experience rice containing sufficient of these external layers surely to prevent beriberi can be selected by this method

Rice may be subjected also to chemical analysis for the same purpose In addition to vitamin B the greater part of the phosphorus contained in the grain is located in the external layers and is removed in the polishings by the milling process and the amount of phosphorus pentoxide remaining in the rice has been used as an indicator to show how completely the external layers have been removed This standard has the advantage that it can be established definitely by law whereas visual examination must remain a matter of judgment and experience but it entails the employment of a chemist and in later years there has been much discussion concerning an adequate chemical standard The standard of 0 4 per cent phosphorus pentoxide was proposed originally by Fraser and Stanton in 1911 While this standard is generally satisfactory after several years observers began to point out instances in which beriberi had occurred among patients fed on rices that conformed to this standard and other standards of 0 5 or 0 6 per cent phosphorus pentoxide were suggested Practically all the fat of the grain is located also in the external layers of the grain In 1927 Vedder and Feliciano published the results of a study of 200 rices from different localities and of all degrees of milling the beriberi producing potentialities of these rices being determined for each one on a group of 4 pigeons for 100 days Pigeons may develop polyneuritis on a very deficient rice as early as 15 days The chemical index proposed as the result of this study was any rice having 1 77 per cent of phosphorus pentoxide plus fat but not less than 0 4 per cent of phosphorus pentoxide or any rice having not less than 0 62 per cent of phosphorus pentoxide No rice possessing these requirements produced polyneuritis in pigeons and this standard excluded only 9 rices out of 200 that afforded protection to pigeons

With regard to the general population the case is quite different The native races who suffer from beriberi subsist chiefly upon highly milled rice This is partly a matter of racial food habit but largely an economic question Rice is milled and polished chiefly because it can be stored more readily in this form Undermilled rice is prone to become infested with weevils moths and other insects that also appreciate the food value of the external layers Although it has been found experimentally that this may be prevented by planting bottles of carbon tetrachloride or chloroform in the sacks this method is hardly practical

Before the introduction of thiamin venesection was the best remedy First recommended by Anderson in 1887, venesection was often practised with good results and venesection still is life saving in other cardiac decompensation due to right ventricular failure In beriberi at the present time the use of thiamin is preferable and the results often are dramatic

All adult cases should be given a high protein high vitamin diet with severe limitation on the amount of rice consumed This should always be of the under milled variety called brown rice in the United States

PROPHYLAXIS

It has been demonstrated that beriberi may be eradicated when it exists and prevented from occurring by the use of undermilled or cured rice or by the addition of various varieties of peas and beans or barley to the ration of rice Beriberi was eliminated from the Philippine Scouts by the simple plan of issuing an undermilled rice in place of the decorticated rice previously used Undermilled rice has been issued continuously since 1910, and for the past 25 years beriberi has simply ceased to exist as a cause of admission to sick report, although these troups are surrounded by other Filipinos who suffer from that disease The Japanese prevented beriberi by mixing 10 ounces of whole barley with each 20 ounces of rice The daily addition of 4 ounces of a legume (katjang idjoe) was tried in the Dutch Indies and produced the same result On the whole the best results have been obtained with undermilled rice which the native must eat or go hungry, rather than by the addition of legumes, which some dis like and will not eat Beriberi rarely if ever, occurs when a sufficient amount of meat, eggs, fresh milk and fresh vegetables are used Bremaud and Laurent both claimed in 1889 that under certain circumstances fat in the ration prevented beriberi While fat probably contains no thiamin some fats at least recently have been found to exert a sparing action on the demand of the body for that vitamin Thus pork has been given thiamin index of 30 as compared with 5 for beef and mutton The inclusion of pork in a ration is therefore to be recom mended as a preventive against beriberi The prevention of beriberi theoretically is therefore simple in the extreme, and success or failure is a matter of adminis trative technique

Among native troops and government institutions the problem is simple, because the use of the highly milled and beriberi producing rice can be for bidden by order and the use of undermilled rice enforced This action alone has eliminated beriberi from all governmental institutions in the Philippines

When an undermilled rice is thus ordered for the prevention of beriberi each lot of rice purchased must be examined by some central authority to be sure that the germ and sufficient of the external layers of the grain remain

subsequently at length by Guerrero and Quintos, by Albert and by Andrews It has been found that a large part of the infant mortality in the Philippines is due to this disease and consequently the mortality among breast fed babies is very high whereas in Europe and America breast fed babies usually thrive and the heaviest mortality occurs among infants that are artificially fed

Etiology

That the disease is transmitted by the mother s milk has been recognized from the first account written by Hirota Only children that are breast fed suffer from the disease Often a mother has had several successive children die of beriberi and it is not unusual to find mothers who have lost children in this way and then have saved others by artificial feeding Indeed after the infant has developed beriberi merely removing it from the breast and feeding it cow s milk will restore it to health if the disease has not progressed too far Moreover Andrews showed that puppies developed beriberi when fed exclusively on the milk of women whose children had died of infantile beriberi

It was suggested by Hirota and very generally accepted that some toxic substance was secreted in the milk of mothers suffering from beriberi This as well as a toxin to account for adult beriberi was a plausible theory in the years before the demonstration of a series of deficiency diseases in animals No such toxin could be isolated or demonstrated while on the contrary Chamberlain and Vedder in 1912 succeeded in curing a number of cases of infantile beriberi by administering to the infant an extract of rice polishings which previous experiments had demonstrated would prevent polyneuritis in fowls fed exclusively on polished rice During this treatment the infants continued to receive their mother s milk as the only food Recovery in these cases was as prompt as the cure of scurvy by lemon juice and was so definite that the curative effect of the extract could not be doubted The conclusion is inevitable that this curative effect was due to the supply of vitamin known to be present in the extract rather than to the neutralization of a toxin in the milk It is now recognized that infantile beriberi is the purest form of thiamin deficiency

Pathology

The gross anatomy is practically identical with that of adult beriberi and includes

1 A greatly hypertrophied and dilated right heart The musculature is coarse and firm and the right heart forms much the larger part of the organ even in the contour of the apex The wall of the right ventricle may measure from 5 to 7 millimeters in thickness while the wall of the left ventricle measures

in the thousands of sacks of rice stored in warehouses In practice undermilled rice must be kept unhusked and milled frequently so that it can be used before it deteriorates and this increases the price of the rice Beriberi could be prevented also by the addition of a reasonable amount of the beriberi preventing foods, already mentioned, to the diet of rice It has been found that servants gladly eat these foods when they are provided, and beriberi is rare among natives, who are sufficiently prosperous to buy good food The existence of beriberi, therefore like many other diseases is really caused by poverty and the best method of prevention is such economic measures as will diffuse a greater prosperity

R R Williams has devised a method of enriching highly milled rice with thiamin so that this rice will contain more thiamin than any undermilled rice, and the contained thiamin will withstand both washing and cooking Either parboiled rice, undermilled rice or thiamin enriched white rice will prevent beriberi

Outbreaks of beriberi have occurred also somewhat infrequently in countries like Labrador and in various institutions in the United States and Europe such as insane asylums almshouses and prisons Apparently all of these outbreaks have been due to the excessive use of white bread Bread made from decorticated wheat is quite as deficient in vitamin B as decorticated rice and produces polyneuritis in birds with the same regularity Flour since 1940 has been standardized by the Food and Drug Administration "Enriched' white flour must contain nicatinic acid thiamin and iron in amounts equal to those of whole wheat flour

PART II

INFANTILE BERIBERI

Definition — Infantile beriberi is true beriberi affecting infants, who are breast fed and whose mothers suffer from manifest or latent beriberi Like beriberi in adults it is caused by the same vitamin deficiency in the diet which in this case is the milk of a mother whose diet is so deficient that she is unable to excrete these vitamins in her milk It is characterized clinically by a mild peripheral neuritis generalized edema and especially, by cardiac hypertrophy and acute dilatation resulting in sudden death

History

It was formerly believed that young infants never suffered from beriberi but infantile beriberi was first described by Hirota in Japan in 1898 Infantile beriberi was recognized in the Philippines by Guerrero in 1904 and was described

is sharper and considerably accentuated indicating increased pressure in the pulmonary *circulation although the blood pressure in the systemic circulation* is very low In this condition the child may die suddenly after a few minutes or it may recover only to die after a few days as the result of a similar cardiac crisis This clinical picture of acute beriberi in infants is practically identical to that seen in so called acute pernicious beriberi in adults Like these adults the child probably has suffered from slight edema or a mild peripheral neuritis for some time but in the infant these symptoms escape notice entirely and the sudden dilatation of the heart is the first and often the last symptom that is observed

Chronic infantile beriberi is not so common In such cases the cardiac symptoms are less severe although when the condition is *well* developed the heart will be found to be enlarged and the second pulmonic sound accentuated while the pulse is rapid and soft and the blood pressure low The earliest symptoms usually are vomiting and obstinate constipation which does not yield readily to treatment The vomiting is repeated several times a day at irregular intervals The child loses weight becomes very restless and fretful and whines continually especially at night so that it rarely sleeps well As these symptoms persist in spite of various treatments the child becomes quite pale and presents a peculiar waxy appearance which is quite characteristic Com bined with these symptoms is a great weakness of the limbs which are soft and relaxed

Edema of the limbs may or may not be found but some excess of fluid fre quently is found at necropsy if not during life Comparatively late in the disease the child often suffers from aphonia or loss of the normal voice although it still cries with a peculiar whine that is almost pathognomonic This corresponds to a similar loss of voice observed in adult cases and probably is due to degeneration of the pneumogastric nerves

The clinical picture of beriberi in infants is therefore quite similar to that observed in adults if we remember that in the infant only objective symptoms can be elicited

Prognosis

The prognosis is very bad if the infant continues to be fed exclusively on its mother s milk Under such circumstances practically all of these infants *die But when proper dietary treatment is instituted* the majority of cases re cover

Treatment

From the first accounts of the disease it was recognized that medical treat

only from 3 to 5 millimeters Congestion of all the abdominal viscera with subpleural hemorrhages and a certain amount of pulmonary edema are the direct result of the cardiac weakness and the acute cardiac death

2 General anasarca combined with effusions Effusions into the pericardium and peritoneal cavity are most frequent The fluid is clear and of a greenish tint

3 Degenerative changes in the nerves, which especially in acute cases usually are less marked than is the case in adult beriberi, probably for the reason that death occurs so promptly in the infant

In addition to this combination of findings, which is characteristic of beriberi it may be emphasized that there are no other pathological changes to account for death

Depletion Period

Infantile beriberi may appear soon after birth and approximately 80 per cent of the cases occur during the first 3 months of life It is quite rare after the fifth month Bearing in mind that the depletion period in adults is between 3 and 4 months the shorter period in infants may be explained by the well known fact that all young and rapidly growing animals develop deficiency diseases much more rapidly than adults, and for this reason young animals are used in experimental work It is also possible that in some cases the deficiency may have existed in utero The mother, who is suffering from a similar dietary deficiency, may be unable to supply the fetus with thiamin in sufficient quantity during the last months of pregnancy when the child is growing rapidly

Symptomatology

There are two types of infantile beriberi, acute which is generally wet and chronic which is more apt to be dry Acute infantile beriberi is characterized by the extreme rapidity of its onset The only warning is that in most of the cases the urinary secretion is markedly diminished, and because of this and of constipation the number of napkins used is greatly diminished A young breast fed infant of from 1 to 3 months of age who previously has been apparently normal and healthy aside from the small urinary secretion and who seems particularly well nourished is seized suddenly with an acute cardiac paroxysm The child appears to be in great pain cries constantly straightens out its body and becomes quite rigid The face becomes cyanosed and the pulse is small rapid and irregular Some edema generally can be found especially in the lower limbs, and when the heart is examined it is found to be considerably enlarged and the heart sounds rapid and irregular The second pulmonic sound generally

Prophylaxis

The prevention of infantile beriberi is exactly the same as the prevention of the disease in adults If the mothers are properly fed during pregnancy and lactation the children will not develop beriberi When it is known that the diet of the mother is deficient a prophylactic dose of thiamin chloride 5 to 10 milligrams should be given daily to the mother and proportionate daily doses to the infant until it is 6 months of age

PART III

SHIP BERIBERI

True Asiatic beriberi has occurred frequently on ships whose crews were Orientals and whose staple diet was rice and this may be expected to continue However what is generally known as ship beriberi was a disease affecting European or American crews of sailing ships after long voyages

The sailors on Norwegian ships suffered from ship beriberi more often than the crews of other nationalities but since the sailing ship has practically disappeared and steamships are provided with cold storage and make much shorter voyages ship beriberi like scurvy has disappeared and interest in it is chiefly historical

Etiology

The cause of the disease is undoubtedly to be found in an improper and one sided food supply At best the food used on such long voyages was very monotonous consisting chiefly of wheat flour cooked in various ways and salt meats In some cases the food became spoiled and a Norwegian commission appointed to determine the cause of ship beriberi came to the conclusion that it was caused by spoiled preserved food But many cases of ship beriberi are known to have occurred when no spoiled food was consumed and vice versa extreme spoilage usually has not produced ship beriberi It is now known that ordinary white wheat flour is quite as deficient in vitamins as is rice and will produce beriberi in man and polyneuritis in fowls We also know that a diet of bread and soup can produce dropsy for in 1847 the most frequent cause of death in 41 prisons in England France and North America was what was then known as prison dropsy and a similar diet was responsible for war edema in the prison camps during the late war The conception that ship beriberi is a deficiency disease similar to or identical with true beriberi is more in accord with the facts In some of the instances when spoiled meats could not be eaten it may have been associated with edema caused by protein deficiency In some instances symptoms of scurvy also were present

ment was merely symptomatic and palliative In accordance with the theory that the child was receiving a toxin in the mother's milk Hirota and physicians in the Philippines insisted on the necessity of weaning the child and substituting artificial feeding for the mother's milk This treatment is satisfactory when it can be carried out properly but among poor natives, whose children are the chief sufferers, it is impracticable owing to the cost of good milk and ice, and in addition the supply of fresh cow's milk is extremely limited in the Philippines, because the cows die of rinderpest Many of the infants so treated die of infections resulting from the use of dirty milk

Chamberlain and Vedder found that these infants can be saved by administering an extract of rice polishings to the child If this is done, it is not necessary to wean the child, and this treatment ensures the advantages of breast feeding

The extract may be prepared as follows The rice polish is extracted with 6 times its bulk of 90 per cent alcohol and the alcoholic extract is evaporated in the cold by an electric fan or at reduced pressure in a vacuum The residue is placed in a separatory funnel, and the fat which rises to the top is discarded The brown syrupy residue is diluted with a small amount of water to a convenient dosage and the resinous precipitate filtered The child should receive daily the extract from about 100 grams of rice polish, which usually will be from 5 to 10 cubic centimeters of the extract When properly prepared the extract is sweet and pleasant to the taste and can be administered easily even to the youngest infants with a medicine dropper

Improvement generally is immediate The vomiting stops in from 24 to 36 hours edema disappears in the course of a few days, and the child urinates freely and sleeps well The cardiac symptoms also clear up in a few days, and the cardiac hypertrophy is reduced, so that in 7 to 10 days the child is entirely well except from the effects of peripheral neuritis These symptoms including aphonia do not disappear until the treatment has been continued for several months However great improvement in cardiac and dropsical symptoms usually was noticed after one or two days' treatment This prompt recovery, while continuing to use the mother s milk is conclusive evidence that the condition was not caused by a toxemia and the fact that no protein deficiency was found in the milk and that the condition was cured by a non protein extract, disposes of the theory that the edema is caused by protein deficiency

This treatment proved so successful that ever since 1912 large quantities of this extract have been prepared at the Bureau of Science in Manila for free distribution to the natives Wells in 1921 reported that up to the end of the year 1920 47 530 bottles of 50 cubic centimeters each had been prepared and issued Since 1938 cases have been treated by injections of thiamin chloride with equally satisfactory results

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Symptomatology

As deaths from this disease almost always have occurred at sea on ships not provided with medical attendance, there has been practically no opportunity for post mortem investigation, especially since most of the cases that reach shore recover but such cases have been investigated clinically, and a fair picture of the symptomatology has been secured

The disease begins with loss of appetite, nausea obstinate constipation and other gastrointestinal disturbances Soon there is a feeling of general weakness, and a dropsical swelling appears about the feet and ankles which progresses slowly but steadily up the legs and even to the abdomen and chest in some cases The patients complain shortly of a feeling of numbness in the feet and of inability to walk far

This indisposition to exertion is not only due to the condition of the legs but also to the shortness of breath and palpitation of the heart which develop at about the same time The increasing dropsy and shortness of breath finally compel the victims to remain in bed, and death is by no means uncommon apparently caused by heart failure with the same clinical picture as seen in beriberi as described earlier in this chapter

As soon as the symptoms have once appeared, they increase in severity, and additional cases continue to develop among the crew But if the ship reached port and secured fresh food the invalids all commenced to show improvement so that in from 1 to 2 weeks the majority had apparently recovered In a few such cases a peripheral neuritis remained which disappeared only slowly under dietary treatment

The symptoms of ship beriberi appear to coincide with those of true beriberi except that in the former the symptoms of peripheral neuritis, as a rule, appear milder, while there is a greater tendency to dropsy and effusions In other words the condition is more like that form of beriberi known as wet, and so it is probable that ship beriberi is merely one form of true beriberi in which there is a great tendency to the wet type of the disease The question naturally arises if this is not also the case in epidemic dropsy The mortality of ship beriberi may be quite high if the voyage continues long after the development of the cases Of 947 cases observed in 158 ships there were 147 deaths or an average mortality of 14 4 per cent

Treatment

It is generally agreed that all cases except those already moribund recover when they receive a properly balanced diet including fresh meats and vegetables No other treatment is required

Prophylaxis

The rules given for the prevention of beriberi apply here with such modifications as are necessary to a food supply to be carried on a ship not having cold storage facilities Bread should be made from whole wheat and beans and peas should be carried with as many potatoes as can be used before they spoil

PART IV

EPIDEMIC DROPSY

Definition — Epidemic dropsy may be a deficiency disease closely related to beriberi It is characterized clinically by dropsy often associated with cardiac symptoms similar to those occurring in beriberi but without marked paralysis or anesthesia The deficiency occurs on a diet whose staples are rice and dal (legumes belonging to the genus *Phaseolus*)

History

In 1876 during a famine in India a disease appeared whose principal feature was dropsy but it was first described as beriberi The term epidemic dropsy was first employed by MacCleod as a designation for the dropsical disease which occurred in Calcutta in the winters of the years 1877–1880 It was also observed in Mauritius in the year 1878–1879 but according to Megaw these cases occurred in coolies from Calcutta and their food also came from India However that may be it was described there by Fayrer as beriberi Since that time the disease recognized as epidemic dropsy has recurred annually to a greater or less extend in various parts of India including Madras Assam and Bengal Two great outbreaks occurred in Calcutta in the years 1909 and 1926 and it is from these cases in Calcutta that we derive most of our information In 1908 Pearce stated his belief that epidemic dropsy is beriberi and in 1912 Greig concluded that epidemic dropsy is a deficiency disease Megaw in 1927 believed on the contrary that epidemic dropsy while closely related to beriberi has certain features that differ from it including fever skin eruptions and often glaucoma

East Indian investigators very generally have attributed epidemic dropsy to the toxic effect of *Argemona mexicana* a common adulterant of the mustard oil used in cooking Argemona is toxic to animals but I am not convinced that epidemic dropsy has been produced by these seeds It remains possible that the use of toxic mustard oils may account for the differences found by Megaw between wet beriberi and epidemic dropsy

While epidemic dropsy certainly is found mainly in India, Mann in 1924

described an edema disease" in Haiti, which was dissipated by an improved diet Similar cases have been reported from the Dutch Indies

Etiology

The term is a misnomer, for all authorities now agree that the disease is not infectious but is caused in some manner by the diet some believing it to be a simple deficiency while others like Megaw think it is caused by an intoxication from rice that has been improperly stored With regard to the diet of 594 cases investigated by Greig decorticated rice was the staple food in all cases but curiously enough if the rice were toxic, the majority of the cases occurred among those eating 2 4 or 6 ounces and was very rare among those eating from 10 to 16 ounces daily All 594 cases used dal, but here again the majority of the cases were among those who consumed from 1 to 2 ounces daily and was much less frequent among those who consumed from 2 to 3 ounces 508 of the cases used ata which is a coarsely ground whole wheat flour, but 505 cases used this flour finely sifted which means that the majority of the external layers of the grain were removed while only 3 cases, who consumed the coarse ata, were affected These facts all point toward food deficiency and Greig showed that the epidemics commenced and declined with the rise and fall in the price of food grains It appeared probable that, as the price of grain rose the natives could not afford to purchase the supplementary articles of diet that protect such as milk and vegetables and living nearly exclusively on deficient foods, the disease appears whereas when the price of grain falls they are again able to purchase the supplementary articles and the disease disappears But the price is lowest when the new harvest is in, and consequently the disease only occurs some time after the harvest or, according to Megaw, after the rice has been kept for some time and has become toxic The same set of facts obviously can be interpreted both ways but to the writer it appears that the deficiency theory is far more probable, and that the facts conform to what is known concerning other undoubted deficiency diseases When it is added that Greig found 52 cases of scurvy in 630 cases, the deficient diet is made almost a certainty

Megaw states that the disease only occurs among rice eaters and this is undoubtedly true for India but if the edema disease described by Mann was epidemic dropsy it occurred on a diet consisting of cornmeal and lard with no rice In this outbreak over 1 000 prisoners died from this affection although as Mann states there has been no case of this edema disease noted in any of the personnel of the gendarmerie during the past six years '

It is generally believed that this edema is not caused by deficient protein as is true for prison dropsy and war edema Yet it must be remembered that

the strict Hindu will eat no meat or fish although he will use milk and protein deficiency cannot be absolutely excluded

The natives who develop epidemic dropsy are all rice eaters and some should therefore develop beriberi and in fact beriberi does occur The majority eat dal and if they eat sufficient will be protected against beriberi Those who do not eat sufficient dal when the price of rice is high will develop wet beriberi or if in addition they use contaminated mustard oil will develop epidemic dropsy and it is easy to see how these cases might correspond to the consumption of certain rices The fact that epidemic dropsy originally was considered to be a form of beriberi lends support to this view

Pathology

Comparatively little is known concerning the pathology owing to the prejudice in India against post mortem investigations and very few necropsies have been recorded Edema is present in the subcutaneous tissues particularly of the legs and feet but often in the entire body Serous effusions are common The lungs are congested and edematous and the heart usually is enlarged and dilated The stomach and duodenum are congested and present numerous injected areas or ecchymoses The liver and kidneys also are much congested These lesions are the usual pathological findings in cases of wet beriberi

Symptomatology

Epidemic dropsy differs from the wet type of beriberi in that (1) fever is common (2) hemorrhages are common (3) glaucoma is common These exceptions require some discussion

Epidemic dropsy frequently is described as beginning with fever the temperature rising from 99 to 104 F and this fever lasts a variable time with intermissions That fever is no essential part of the disease is indicated by the fact that Creig found fever recorded in only 3 2 of 630 observed cases In a country where almost all have malaria at some time and where many other infections are common fever in a considerable percentage of cases is to be expected In these 630 cases 12 septic infections 1 pneumonia and 4 cases of dysentery were recorded Malaria the commonest disease of the tropics is not mentioned

Hemorrhages are no part of the picture of beriberi but are characteristic of scurvy Of these 630 cases the interesting fact was noted that 52 or about 8 per cent suffered from manifest scurvy with characteristic stomatitis and bleeding from the gums with hemorrhages from the bowel The skin lesions described as a rash by some observers consist of petechiæ or small cutaneous

hemorrhages and a mottling over the edematous parts These are also frequent, if milder symptoms of scurvy, which occurred in 180 out of 630 cases

Recently it has been claimed that glaucoma responds promptly to the administration of the hormone of the adrenal cortex cortin The result of a deficiency of cortin is a sharp disturbance of the water salt metabolism and a rapid increase in the secretion of fluid in the eye results in a rapid rise in intra-ocular tension A similar disturbance of the water metabolism is the characteristic feature of epidemic dropsy

Excluding fever and the skin manifestations hemorrhages and glaucoma, the remaining symptoms are quite typical of beriberi

Apparently the only characteristic and constant symptom of epidemic dropsy is the dropsy and this occurs early and usually is the first symptom It appears first almost invariably in the subcutaneous tissues of the feet and legs and may be confined to these parts but often progresses to the trunk and upper extremities The face is affected rarely In the same 630 cases edema occurred in the feet alone in 8 cases, in the feet and legs in 442 cases in the legs and hands in 37 cases and in the entire body in 129 cases Usually the anasarca remains for a long period Some few cases recover in one or two months but in 40 per cent of Greig s cases the edema remained for from 3 to 4 months, and in 25 per cent of the cases the condition lasted for from 5 to 6 months Not infrequently there is effusion into one of the serous cavities, the pleura pericardium or peritoneum

Associated with the dropsy in many cases are three classes of symptoms, those dependent on cardiac disturbances, those dependent on gastrointestinal derangement and those due to impairment of the nervous system

The cardiac symptoms are dyspnea palpitation and precordial pain Of 630 cases 364 suffered from dyspnea, 102 from palpitation alone and 4 from pain and palpitation None suffered from pain alone It will be seen that the cardiac symptoms in general are not so severe as in beriberi, yet occasionally dilatation of the heart may occur, and sudden death from cardiac failure is the usual cause of the fatal termination that may occur in from 2 to 5 per cent of cases The cardiac disturbance combined with dropsy and muscular weakness may persist for months causing partial or complete incapacity for work

Gastrointestinal symptoms include vomiting diarrhea and loss of appetite Of 630 cases 282 presented such symptoms and in 35 the vomiting and diarrhea were profuse The nervous symptoms include alteration in the reflexes some wasting and tenderness of the muscles and occasionally slight anesthesias No alteration in the reflexes was found in about 80 per cent of the cases studied but in the remainder the knee jerk was either increased or diminished Tenderness of the muscles of the calves was found on pressure in about 30 per cent of the cases and some emaciation and muscular weakness in about 24 per cent

Anesthesias are more uncommon These are the symptoms of dry beriberi which are absent entirely in the majority of the cases and when present are usually very mild as compared with true beriberi

A moderate anemia is found in pronounced and long standing cases the red count falling to between 3 to 4 millions with a proportional decrease in hemoglobin The leucocytes may be somewhat increased but the differential count is normal

The urine is normal except for a low specific gravity in cases of generalized edema it was found to average 1 003 It contains no albumin or casts

Complications

Septic infections and dysentery have been recorded Probably such patients have an increased susceptibility to all infections and latent malaria may become manifest Scurvy can hardly be called a complication as its symptoms appear to be a regular part of the clinical picture Scurvy and beriberi often occurred simultaneously in ship beriberi a condition that is inevitable on a one sided diet of rice or bread without vegetables and fruits That beriberi and scurvy are so seldom seen combined is due partly to the bountiful supply and cheapness of fruits in most of the countries where beriberi is endemic and partly to the fact that the depletion period for scurvy in man is somewhat longer than that of beriberi

Prognosis

This is generally very favorable especially if the proper dietary changes be made for recovery is the rule although from 2 to 5 per cent may die Relapses sometimes occur Of the 630 cases 26 suffered one relapse 2 suffered 2 relapses and 3 suffered 3 relapses Probably if cases were followed for several years it would be found that many of them suffer from recurrent annual attacks

Treatment

A full and generous diet including reasonable amounts of milk meat eggs vegetables and fruits should be prescribed If caste or religion prohibits the use of meat the same result probably could be obtained by increasing the amount of milk or of dal and other legumes for the evidence indicates that these afford protection when eaten freely Rice should be excluded as it is deficient even though it is not toxic as is believed very generally If absolutely demanded it should be undermilled or parboiled Experience indicates that patients cannot be trusted to eat the required diet in their homes and hospital treatment is to be preferred In numerous instances epidemic dropsy has improved very rapidly after the institution of a proper hospital diet

PART V

BERIBERI AND MALNUTRITION

That a diet consisting mainly of white bread will produce beriberi has been known for a long time Little reported 220 such cases in Labrador in 1914 and Aykroyd reported a similar case from Newfoundland in 1930, but the cases discussed here are somewhat different

Kepler in 1925 reported a case of beriberi in a negress who voluntarily restricted her diet to raw starch, eating from 1 to 2 pounds daily At the end of 3 years polyneuritis with some edema and an enlarged heart developed The diagnosis of beriberi was made, and autolyzed yeast was given followed by recovery Here was a diet that must have been deficient in all vitamins Why it required 3 years to produce beriberi and why beriberi instead of some other deficiency disease can only be explained as the result of great individual resistance This is a particularly good illustration of the fact that probably few human diets are well balanced with the exception of the deficiency of a single vitamin and hence the superiority of animal experiments in which such diets can be planned

Urmy Ragle Allen and Jones in 1934 reported beriberi occurring after a short circuit operation on the small intestine The condition was cured by disconnecting the intestinal anastomosis Two similar cases are mentioned In one beriberi developed in a patient with ulcerative colitis and an ileostomy, and in the other the neurological symptoms of beriberi appeared 2½ years after an enterostomy between the stomach and the lower ileum In these 3 cases vitamin B deficiency undoubtedly was produced as the result of lack of absorption Inability to utilize vitamin undoubtedly will produce the same result as a deficiency in the diet Such cases can hardly be common because even when gastroenterostomy is performed so large a portion of the small intestine rarely is short circuited However, surgeons should keep this possibility in mind

In 1933 Brauchle reported a case in a vegetarian woman of 60 who developed polyneuritic symptoms with pronounced edema probably beriberi In 1934 Riesman and Davidson reported a case, diagnosed as beriberi, in an old man, who had voluntarily restricted his diet because of a stomach disorder He eliminated one article after another from his diet until a year and a half before admission he lived on milk exclusively He drank 3 quarts of milk daily for some time but finally reduced this quantity considerably His chief symptoms were very extensive edema with tenderness of the muscles and ecchymotic spots on legs and buttocks The latter symptom suggests scurvy The edema in this case may have been caused by beriberi but hunger edema must be considered

Famine, war or hunger edema or prison dropsy has been defined as a form of dropsy associated with bradycardia, asthenia and polyuria It occurs in

persons subjected to prolonged underfeeding rather than in those with deficiency of any particular vitamin Schittenheim and Schlecht who investigated an out break in a labor corps during War I concluded that it was caused by protein starvation combined with excessive intake of fluids This is in accordance with the work of Maver and of Kohman Kohman produced edema in rats fed on a diet containing only such protein as was contained in carrots with butter fat and wheat germ being given as sources of vitamins A B and D Mineral salts were included also The addition of purified casein to the diet prevented the appearance of the edema Frish Mendel and Peters repeated this work in 1929 demonstrating that such low protein diets give rise to a low protein content of the serum However edema did not occur even if the serum proteins were low unless there was a considerable water intake We may conclude therefore that hunger edema is caused by a diet deficient in proteins with a large fluid intake

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CHAPTER XIII

PELLAGRA

By Frederick R. Taylor and David Cayer

Table of Contents

Synonyms — Alpine scurvy Asturian leprosy Asturian rose calore del fugato Casal s disease disease of the Landes erythema endemicus Italian elephantiasis Lombardian leprosy Lombardy erysipelas maladie de Teste mal de la rosa mal della spienza mal del sole mal de misere medismus mentagra pellagra des Landes pellarina psilosis pigmentosa psychoneurosis medica St Aman s disease scorbutic palsy scorbuto alpino scorbuto montano scottura di sole scurvy with sunburn the red death

Definition — Pellagra is a disease which is generally believed to be due primarily to a specific nutritional deficiency although certain predisposing and precipitating factors play a role in the pathogenesis It manifests itself in symptoms affecting chiefly the skin the alimentary tract and the nervous system

History

Much more research is needed in the history of pellagra The time of its earliest recognition is unknown In his original chapter on pellagra in this work Wood noted that Hippocrates description of *sollicitudo* often has been thought to represent pellagra but that the absence of any skin lesions makes this doubtful According to Sambon the elder Pliny, describing *mentagra* in the 26th book of his Natural History makes the following striking record, occupantem multis et latius totos utique voltus, oculis tantum immunibus, descendentem vero et in colla pectusque ac manus foedo cutis furfure"

Excluding the above accounts the earliest descriptions available are those of a disease known by names coined by the people indicating that the condition was an old curse The term *mal de la rosa* used by Casal, was coined by the Asturian peasants The term *pellagra*, first used in the literature by Frapolli was an old one meaning 'rough skin' We have no evidence that any medical man claimed the introduction of the word, nor can it be said that any of these 18th century observers regarded the disease as a new one

The case of St Francis of Assisi, recorded in 1224 has several points suggestive to some of pellagra He lived in a district which has been pellagrous in recent times, and pictures of him portraying the famous "stigmata' show marks on the backs of his hands and the tops of his feet suggestive of the usual distribution of the skin lesions In addition he was known to be subject to severe attacks of melancholia but evidence that he was a pellagrin is by no means complete It has been claimed that as early as 1578 there were hospitals established exclusively for the treatment of pellagrins There are, however, many chances of error due to the nomenclature of skin affections at that period

The first accurate account of pellagra is that of Gaspar Casal dated 1735 and published posthumously in 1788 Casal was a physician of Oviedo and became protomedicin de Castilla and physician to Philip V He called the disease *mal de la rosa* and described it as a peculiar kind of leprosy His observations were made on 8 cases His plates depicting the skin lesions of the backs of the hands the tops of the feet and the collar with a manubrial projection leave no reasonable doubt of the identity of mal de la rosa and pellagra The term "Casal s collar' is in frequent use today Strangely enough it was not until 1845 that the Italian and French writers accepted the mal de la rosa" of Casal as identical with the pellagra' of Frapolli Before the publication of Casal's paper Thiery met him in Madrid and was shown cases of mal de la rosa On returning to Paris Thiery wrote his *Description d une Maladie appellé Mal de la Rosa aux Asturies* which appeared in the 2nd volume of Vandermonde s *Recueil Periodique d Observations de Medicine de Chirurgie et de Pharmacie* for May, 1755 He gave Casal full credit for priority

In 1771 Irancisco Irapolli a physicrn of the Hospital Majeur in Milan published his *Inimadversiones in morbum vulgo pelegram* This was the first record of the word pellagra although the spelling varied Four years later Francisco Zanetti a physician of Canobia recorded the appearance of the disease on the shores of the Lago Maggiori thus Nemo quem ipse sciam usque adhuc de haec cutis affectione peculiariter scripsit He stated that the condition was called pellagra and occurred chiefly among the poor and malnourished In 1776 Jacopo Odoardi a physician of Bellune referred to pellagra under the name *scorbuto alpino* About the same time Antonio Pujati a professor in the University of Padua described the disease under the names *pellarina scottura di sole calore del fugato* and *mal della spienza* He regarded it as a kind of scurvy occurring in the subalpine country In 1780 Michel Gherardini another physician of the Hospital Majeur as Frapolli had been wrote a very valuable account of the disease The historically important paper of Albera which Roussel referred to as mystico scientific appeared about this time

Kaiser Joseph II of Austria founded a special hospital for the treatment of pellagra in 1784 which was placed under the charge of Gaetano Strombio In *1788 it was abandoned and Strombio was placed over a greater special hospital* established in Milan His work *De Pellagra* appeared in 3 volumes in 1786–89 He had abundant opportunities at his disposal and his work always will remain of great importance He has been regarded by many as the greatest clinical authority on pellagra

The work of F Fanzago in 1789 furthered the trend towards the recognition of the identity of alpine scurvy and pellagra and later Roussel showed mal de la rosa and pellagra to be the same affection In 1791 Sartago described *scorbuto montano* occurring in the region of Aviano According to Strombio s description this disease also was pellagra It was recognized the same year in Piedmont by Allioni Seale Harris Jr states that in 1792 Cherardini produced skin lesions in pellagrins by exposure to the sun

In 1810 Marzari in his *Essai Medicopolitique* stated that he recognized pellagra in all the new provinces which Napoleon had established beyond the Alps This writer first emphasized the maize theory of etiology although it had been advocated by Strombio and many others of that period At that time polenta was under suspicion as it was almost the sole food of the Italian peasantry It was a thick gruel of maize or corn meal which was allowed to ferment for days after cooking Meat and dairy products according to the writers of this period were conspicuously absent from the dietary of the pellagrin Marzari did not regard polenta as a specific cause but put it in the same class with poor hygiene Writing later Roussel thought this work of great value in connection with his advocacy of the damaged maize theory

In 1830 Briere de Boismont presented to the Academie des Sciences an im

portant paper showing that pellagra was rampant within a few miles of Paris and that its existence was not appreciated properly A few, however were alive to the menace, among them being J M G Hameau of Teste de Buch, whose writings did much good The disease studied by him was proved to have been pellagra although he first called it *maladie de Teste* and later *pellagra des Landes* In 1836 the authorities of the Gironde became alarmed and asked Leon Marchand physician for infectious diseases, to make a new study of the condition He devoted years to the work and in 1843 wrote a monograph for the Paris Academie de Medicine emphasizing that pellagra was a disease of the city, but that workers in the earth and shepherds also were subject to it and that it was a disease of the poorly nourished He found it in all the 20 communes of the Gironde

Elvehjem tells us that in 1830 the census in northern Italy revealed that in many areas 5 per cent of the population were suffering from pellagra He notes that it was endemic in France from 1818 to 1880 but practically disappeared after that date in that country

The writings at the end of the 1st quarter of the 19th century show that pellagra was being confused with other conditions About 1828 acrodynia was described as occurring in Paris in epidemic form All writers granted its striking similarity to pellagra Probably more than one disease was classified as pellagra Even E J Wood at a much later date stated that he had made the diagnosis of acrodynia in a patient who subsequently developed typical pellagra

The idea of the relation of maize to pellagra became so firmly fixed that in 1899 Billod wrote on ' pseudopellagra" the only distinctive point between it and pellagra being that it occurred where maize was not eaten

No consideration of the history of pellagra can ignore the part played by Cesare Lombroso who spent 25 years studying the disease His final conclusion was that pellagra was an intoxication process produced by the action of certain microorganisms notably *Penicillium glaucum* on maize He believed that these organisms, harmless in themselves produced poisonous substances in the kernels of the maize He found that a tincture made from the moulds of spoiled maize contained 3 substances a ruby red oily liquid, a resinous substance and a toxic product which he called pellagrosein Sound maize was found to contain 3 substances also but they differed from the above At this same time Marie isolated substances from diseased corn which he considered chemically analogous to those isolated from spurred rye and small doses taken over a long period produced effects similar to those of ergot given in like manner Besides the *Penicillium glaucum Sporisorium maidis* a hyphomycete also was found on diseased maize and studied It was supposed to produce gastritis and diarrhea in man and in chickens droopiness and a loss of feathers and of weight Lombroso found it only rarely in Lombardy and attached no importance to it

The appearance of pellagra in the United States makes a notable chapter in

medical history Bloom of New Orleans states that the first authentic case was recorded by Dr John T Gray of Utica N Y and a second case was reported orally by Dr Tyler of Somerville Mass both in 1864 He also states what was previously denied by many authorities including Wood that during the Civil War Confederate soldiers in large numbers were similarly affected by a disease then prevalent among the enemy s armies and then Bloom adds a few years afterwards in 1870 many veterans in the South Carolina Asylum at Columbia were stricken This was the report of Dr H N Sloan of South Carolina Dr D S Pope of Columbia says that at least 2 cases occurred in the South Carolina Penitentiary in 1880–85 Bloom adds further that sporadic cases continued to be diagnosed and cites Dr S Sherwell of Brooklyn as reporting a case in 1883 and Dr S Bemiss of New Orleans among others as reporting one in 1889 A case in North Carolina described as psoriasis in 1889 was diagnosed as pellagra by Wood nearly 20 years later by a study of the records R H Bellamy of Wilmington and J B Wright of Lincolnton were the first North Carolina physicians to diagnose pellagra

The first record of pellagra in epidemic form in the United States is that of an outbreak in a negro asylum in Mount Vernon Alabama in 1906–07 in which 88 cases were reported by Search with 57 deaths He stated that before the epidemic a few cases had been noted every summer since 1901 when the patients had been moved to the Mount Vernon Insane Hospital from Tuscaloosa Of the 88 patients in the epidemic only 8 were males Two of them had been in the hospital more than a year The diet was changed and no new cases appeared Following this epidemic in quick succession came reports of other explosive outbreaks in Texas North Carolina and other states The disease soon became a major medical problem in the southern states where it has been prevalent in mental hospitals cotton mill villages and many rural sections although in recent years its incidence has shown a striking decrease and its character has changed materially Osler s genius did much to stimulate interest in the study of pellagra in the South during the early years

In 1910 Sambon who had worked in Italy the United States and the West Indies advanced the hypothesis of an insect vector in pellagra but this has never been proved

Between 1910 and 1930 notable work was done by three groups of workers the Thompson McFadden Pellagra Commission Goldberger and his coworkers in the United States Public Health Service and the Italian Government The field work of the first group was done in Spartanburg South Carolina In their first report they concluded that (a) the eating of sound or diseased maize has no causative relationship (b) the disease was in all probability a specific infection communicable from person to person by means at that time unknown (c) no evidence incriminating any biting insect vector could be found and (d) intimate

association in the household and the contamination of food with excreta of pellagrins might be possible modes of transmission Later this commission concluded that in the cotton mill villages studied the disease spread from a preexisting case as a center that it was transmitted only very short distances and chiefly to those immediately associated with the case, that the frequent use of fresh meats and eggs offered no protection in the area in which the study was conducted and that the daily use of milk seemed to diminish to some extent, although it did not insure fully against the contraction of the disease In a still later report they stated that the installation of a sewer system brought about a decided reduction in the number of cases They concluded that their studies supported their previous view that pellagra is an infection spreading slowly, and that the spread is favored especially by unsanitary methods of human waste disposal

The work of Joseph Goldberger and his coworkers of the United States Public Health Service had for its basis three salient points, (1) that pellagra is essentially of dietary origin, (2) that it depends on the lack of a specific dietary principle which they called the P P (pellagra preventive) factor, and (3) that no pellagra develops in those who consume a mixed, well balanced and varied diet Dr Clarence Pierson of Pineville, La was one of the first men in this country to treat pellagra with a full diet and obtained excellent results which were observed by Goldberger The latter found an orphanage where in 1913 75 per cent of the inmates suffered from pellagra although the children receiving milk escaped He suggested changes in the diet and in the following year among 234 children in the same institution no case of pellagra occurred Similar results were obtained elsewhere

Goldberger then devised a diet which he believed could induce the disease by its deficiency and gave it to volunteer prisoners in a pellagrous district separating them from the exogenous sources of the disease then considered to exist A condition resulted which he and a number of clinicians familiar with the disease regarded as pellagra while others did not, because the skin lesions were on the scrotum It is now known that scrotal lesions are not infrequent in pellagra, and the authors of this chapter believe that genuine pellagra was produced and that lack of exposure to sunlight may explain the absence of skin lesions on exposed parts

Goldberger next gave a number of adult volunteers capsules containing feces of pellagrins without producing any symptoms of the disease He published his first data on pellagra in 1914 His subsequent work not only gave us the strongest arguments for the pure dietary theory of etiology but also marshalled the most formidable array of data against the infectious theory He noted the failure to transmit the disease artificially the fact that doctors and nurses almost never develop it and quoted Kuelz to the effect that during World War I when pellagra was very prevalent in Romania the German army in that country, although in

close enough contact with the Romanian people to contract malaria typhoid typhus and dysentery remained free from pellagra He believed that the pellagra preventing factor was a component of vitamin B which we now know as the vitamin B complex The specific pellagra preventing vitamin now is known as niacin or nicotinic acid although as will be seen later most pellagrins suffer from a multiple vitamin deficiency

A short time before his death Goldberger pointed out an apparent analogy if not identity between blacktongue in dogs and pellagra in man and considered both due to the same dietary deficiency A little later Underhill and Mendel showed that a canine disease practically indistinguishable from the Goldberger type of blacktongue can develop in dogs getting plenty of yeast and red meat and can be cured by giving adequate amounts of cod liver oil whereas cod liver oil has no curative action on the Goldberger type of blacktongue which is cured by yeast and red meat There are therefore two types of blacktongue in dogs one of which is analogous to or identical with pellagra and the other of which is not Smith Persons and Harvey have shown that the oral lesions in both types are identical and due to secondary fusospirochetal infection

Pearson Schmidt and Mackey found that a diet which produces pellagra like symptoms in pigs and blacktongue in dogs had no deleterious effect on lambs In 1940 Heath MacQueen and Spies described an ulcerative stomatitis occurring spontaneously in 6 cats that was relieved quickly by niacin Harris studied pellagra in monkeys

In Italy pellagra was a terrible scourge but the government of that country took measures that reduced its incidence greatly before World War II Many pellagra hospitals were rebuilt and the hospitalization of pellagrins on a large scale apparently was a great factor in controlling the disease Widespread interest was stimulated in raising varied food products notably rice and unemployment was decreased greatly resulting in marked improvement in dietary and economic conditions

In 1912 Casimir Funk first isolated niacin from biological material and attributed appetite stimulating properties to it but it received little attention until Warburg in 1935 showed it to be a hydrolysis product of coenzyme II

The role of alcohol as a predisposing cause of pellagra has an interesting history According to Jellinek Casal is said to have mentioned it Nobili in 1841 attributed pellagrous outbreaks in Italy to abuse of wine Calmarza in Spain in 1870 believed that pellagra was produced by misery and alcohol and several other authors in Spain Italy and France expressed similar views In recent years many studies have been made on this phase of the problem including a notable contribution by Klauder and Winkelmann in 1928 studies continuing to the present time

In 1925 Goldberger Wheeler and Tanner pointed out the value of yeast in the

association in the household and the contamination of food with excreta of pellagrins might be possible modes of transmission Later this commission concluded that in the cotton mill villages studied the disease spread from a preexisting case as a center that it was transmitted only very short distances and chiefly to those immediately associated with the case that the frequent use of fresh meats and eggs offered no protection in the area in which the study was conducted and that the daily use of milk seemed to diminish to some extent, although it did not insure fully against the contraction of the disease In a still later report they stated that the installation of a sewer system brought about a decided reduction in the number of cases They concluded that their studies supported their previous view that pellagra is an infection spreading slowly, and that the spread is favored especially by unsanitary methods of human waste disposal

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Goldberger then devised a diet which he believed could induce the disease by its deficiency and gave it to volunteer prisoners in a pellagrous district separating them from the exogenous sources of the disease then considered to exist A condition resulted which he and a number of clinicians familiar with the disease regarded as pellagra while others did not because the skin lesions were on the scrotum It is now known that scrotal lesions are not infrequent in pellagra and the authors of this chapter believe that genuine pellagra was produced and that lack of exposure to sunlight may explain the absence of skin lesions on exposed parts

Goldberger next gave a number of adult volunteers capsules containing feces of pellagrins without producing any symptoms of the disease He published his first data on pellagra in 1914 His subsequent work not only gave us the strongest arguments for the pure dietary theory of etiology but also marshalled the most formidable array of data against the infectious theory He noted the failure to transmit the disease artificially the fact that doctors and nurses almost never develop it and quoted Kuelz to the effect that during World War I when pellagra was very prevalent in Romania, the German army in that country, although in

close enough contact with the Romanian people to contract malaria typhoid typhus and dysentery remained free from pellagra He believed that the pellagra preventing factor was a component of vitamin B which we now know as the vitamin B complex The specific pellagra preventing vitamin now is known as niacin or nicotinic acid although as will be seen later most pellagrins suffer from a multiple vitamin deficiency

A short time before his death Goldberger pointed out an apparent analogy if not identity between blacktongue in dogs and pellagra in man and considered both due to the same dietary deficiency A little later Underhill and Mendel showed that a canine disease practically indistinguishable from the Goldberger type of blacktongue can develop in dogs getting plenty of yeast and red meat and can be cured by giving adequate amounts of cod liver oil whereas cod liver oil has no curative action on the Goldberger type of blacktongue which is cured by yeast and red meat There are therefore two types of blacktongue in dogs one of which is analogous to or identical with pellagra and the other of which is not Smith Persons and Harvey have shown that the oral lesions in both types are identical and due to secondary fuso pirochetal infection

Pearson Schmidt and Mackey found that a diet which produces pellagra like symptoms in pigs and blacktongue in dogs had no deleterious effect on lambs In 1940 Heath MacQueen and Spies described an ulcerative stomatitis occurring spontaneously in 6 cats that was relieved quickly by niacin Harris studied pellagra in monkeys

In Italy pellagra was a terrible scourge but the government of that country took measures that reduced its incidence greatly before World War II Many pellagra ho pitals were rebuilt and the hospitalization of pellagrins on a large scale apparently was a great factor in controlling the disease Widespread interest was stimulated in raising varied food products notably rice and unemployment was decreased greatly resulting in marked improvement in dietary and economic conditions

In 1912 Casimir Funk first isolated niacin from biological material and attributed appetite stimulating properties to it but it received little attention until Warburg in 1935 showed it to be a hydrolysis product of coenzyme II

The role of alcohol as a predisposing cause of pellagra has an interesting history According to Jellinek Casal is said to have mentioned it Nobili in 1841 attributed pellagrous outbreaks in Italy to abuse of wine Calmarza in Spain in 1870 believed that pellagra was produced by misery and alcohol and several other authors in Spain Italy and France expressed similar views In recent years many studies have been made on this phase of the problem including a notable contribution by Klauder and Winkelmann in 1928 studies continuing to the present time

In 1925 Goldberger Wheeler and Tanner pointed out the value of yeast in the

treatment of pellagra Since 1929 a number of workers have demonstrated the therapeutic value of certain liver extracts The year 1937 was one of the most notable in the history of pellagra for in that year Elvehjem of the Netherlands and his coworkers discovered the value of niacin in the Goldberger type of black tongue and this was followed very quickly by the proof of its extraordinary effectiveness in pellagra thus giving pellagrins, who are all too often the victims of poverty a highly potent yet inexpensive, method of cure An excellent concise report of our knowledge of pellagra to that date by D T Smith was published in the Medical Clinics of North America in March 1943

In 1945 Krehl Teply and Elvehjem, placing rats on an essentially niacin free diet, found that the addition of 40 per cent of yellow corn white corn or corn grits at the expense of the entire ration produced pronounced growth retardation which could be counteracted by adding from 0 5 to 1 0 mgm of niacin per 100 mgm of the ration thus reviving in modified form the old idea that maize may be a factor in producing pellagra Further investigations on this phase of the problem have been carried on by Dann (personal communication)

Distribution and Incidence

Pellagra is distributed widely throughout the world In recent times the countries chiefly affected have been Austria Egypt, France (up to 1880) Italy, Romania Spain the United States and Jugoslavia Although greatly reduced in Italy before World War II it was still an important problem at its onset Its apparent rarity in some of the most severely ravaged European countries since the close of the war will be mentioned further in the section on Etiology It has been noted also in Algeria Argentina Asia Minor Australia, Belgium Brazil Bulgaria, Central Africa Central Asia, Ceylon China Colombia Denmark Germany Greece the Guianas, Hawaii Hungary India Iran Korea the Malay Archipelago Mexico the Netherlands, the Philippines, Portugal Rhodesia Russia South Africa the Straits Settlements, Surinam Thailand Tunisia, Turkey Uruguay and the West Indies, and in many of these countries it has been of more than academic interest It is said to have occurred in New Caledonia and possibly in Central America

In 1866 Roussel wrote 'Recently this malady has invaded new countries and today it is found to the south of 47° north latitude between 10° longitude west and even beyond 25° longitude east, meridian of Paris extending over a long zone of the temperate region of Europe from Cape Finistere to the banks of the Sereth across the Pyrenees provinces of Spain and France upper and central Italy and in the basin of the Danube upon the eastern and southern slopes of the Carpathians even to the frontiers of the Russian Empire

Its course in the United States should teach that it is a very real possibility

to any nation Prior to 1907 in the southern states it was recognized in only very limited areas and there was a marked lack of interest in it Wood noted how reluctant many physicians were to accept his diagnosis and some insisted on refusing to recognize the disease until the seriousness of the situation forced itself on them Among other things it taught the lesson that previous geographic distribution was no obstacle to the appearance of a disease in a region distant from its usual habitat Just as Roussel erred, so did the profession of the United States err in refusing to accept the presence of the Italian disease Since its first appearance it ha been recognized in practically every one of our states so cannot be regarded as a purely subtropical disease

In 1909 a case of pellagra was reported from the Shetland Islands and in 1910 C R Box treated a case in St Thomas Hospital in London Since then a number of cases have been recognized in the British Isles although they have never reached epidemic proportions The disease has acted differently in England than in the United States for in the latter country it soon assumed alarming proportions and it was a very notable fact that our early cases were of a very fulminant type running an acute course of a few weeks and usually ending in death It was really the acute manifestations that misled us in making the first diagnoses for the Italian literature described a chronic disease Greenfield and Holmes state that pellagra is rare in Great Britain especially in children and quote Stannus and Gibson to the effect that there were only 131 published case up to 1934 Hardwick reported 10 cases of pellagra developing in 12 chronic mental patients in a British psychiatric hospital , being schizophrenics 1 a case of dementia 1 an imbecile and 1 a case of paraphrenia as contrasted with 2 cases of psycho es deve'oping in pellagrins As late as 1941 Davis and Hinden gave what they believed to be the first report in England of pellagra superim posed on chronic alcoholism' An editorial in the Lancet in November 1940 stated that, while pellagra following chronic alcoholism was common in the United States it had never been reported in England!

Deeny states that before 1935 only 3 cases of pellagra were recorded in Ireland and that ince that t me up to his publication in 1942 it had not been mentioned in the Irish medical literature despite the abundance of deficiency diseases in that country However he reported 6 cases per se 4 alcoholic cases and 6 cases associated with senility or chronic illness He believes the condition to be relatively common in Ireland and that it is failure of recognition of the disease rather than its rarity that explains the literary lence

It has been impossible to secure accurate data regarding the extent of pellagra in many countries The report of Vice consul W Bayard Cutting gives some striking facts regarding its occurrence in Italy In 1770 the disease was practically unknown in 1839 in Lombardy alone there were more than 20 000 cases and in 1879 over 40 000 In 1881 the provinces of Piedmont Lombardy, Liguria

Venetia, Emilia Marches Umbria Tuscany and Lazio with a total population of 16 689 735 had 104 067 victims While these statistics are recognized as incomplete they show an incidence of 1 case for every 16 of the rural population to which class the disease was largely confined In Italy from the 22 years from 1904 to 1925 inclusive the death rate decreased as follows in 1904 there were 2 363 deaths from pellagra in the kingdom in 1925 there were 108 Taking the four 5 year periods from 1906 to 1925 inclusive we find that from 1906 to 1910 there were 7 725 deaths from 1911 to 1915 4 778, 1916 to 1920 2,919 1921 to 1925 8 4 deaths Cooper points out that in 1899 there were 199 deaths from pellagra per million population in Italy, but after that year there was a rapid and almost constant decline so that in 1925 there were only 3 deaths per million

In Romania in 1901 there were 33 645 cases, in 1905 54 689 cases in 1906 the number exceeded 100 000 According to Marie from whom these figures are taken only 3 cases of this number occurred in Bucharest the disease being almost entirely rural Later reports seemed to indicate that the pellagra mortality might be increasing in urban Romania for in 1923 there were 50 deaths from pellagra in the cities only, in 1924 46 deaths, in 1925 77 deaths and in 1926 172 deaths

Pellagra reached a relatively low level in the southern United States in 1924 but increased rapidly during the period of economic prosperity, reaching a peak in the period 1928–30 Since that time despite a severe economic depression during the period 1931–40 there has been a very striking decrease in the disease

Selwyn D Collins Head Statistician of the United States Public Health Service has furnished us some very interesting data regarding the case rates and death rates per 100 000 population in 13 southern states in which pellagra has been a serious problem These states are Alabama Arkansas Florida Georgia Kentucky Louisiana Mississippi North Carolina Oklahoma South Carolina Tennessee Texas and Virginia The case rates per 100 000 population in these 13 states considered as a single group year by year, from 1929 to 1943 inclusive are as follows

Year	*1929*	*1930*	*1931*	*1932*	*1933*	*1934*	*1935*	*1936*
Case Rate per 100 000 pop	86 2	82 2	84 8	45 1	40 2	27 5	27 1	6 2
Year	*1937*	*1938*	*1939*	*1940*	*1941*	*1942*	*1943*	
Case Rate per 100 000 pop	30 0	39 9	28 7	24 1	21 4	17 2	13 6	

Still more interesting because more accurate are the data regarding the deaths from pellagra per 100 000 population in these 13 states Many non fatal cases go unreported but almost no deaths do so

Year	*19 3*	*1) 1*	*1)*	*1) 6*	*19*	*1)*	*19 9*	*19)*	*1031*	*193*	*1933*
Death Rate per 100 000	9 8	9 4	13	15 9	19 5	22 4	21 5	20 4	16 5	11 7	10 6
Year	*1934*	*1935*	*19 6*	*193*	*1938*	*1939*	*1940*	*1941*	*194*	*1943*	
Death Rate per 100 000	9 4	9	9 5	8 2	8 1	6 0	5 1	4 2	3 5	3 2	

In our own state of North Carolina the total number of deaths from pellagra year by year from 19 0 to 1944 inclusive is especially instructive in view of certain concomitant developments in the state which will be mentioned in more detail under the subject of Etiology Here are the figures supplied by the Bureau of Vital Statistics of the North Carolina State Board of Health

Year	*19 0*	*19 1*	*19*	*19 3*	*19 4*	*19*	*19 6*	*19 7*	*19 8*	*19 9*	*1930*	*1931*	*193*
Deaths	297	331	308	224	273	398	459	712	847	981	1015	896	465
Year	*1933*	*1934*	*1935*	*19 6*	*193*	*1938*	*1939*	*1940*	*1941*	*194*	*1943*	*1944*	
Deaths	3,1	460	,91	356	457	257	208	162	145	116	105	64	

According to Allen in 1914 in a Georgia state hospital the death rate from pellagra was 38 per 1 000 patients with psychotic illness in 1922 it was 12 per 1 000 in 1936 0 He attributes this to the campaign against pellagra begun in 1914 by the United States Public Health Service

DeKleine notes that the highest death rate from pellagra on record for the entire United States was in 19 8 when there were 7 673 deaths of which 7 396 occurred in the 13 states above mentioned As shown in the table already presented this was 22 4 deaths per 100 000 population in those states It was the 8th or 9th highest cause of deaths excluding accidents in 1928–29 in Alabama Arkansas Georgia Mississippi North Carolina and South Carolina Outside of the 13 states mentioned pellagra has never been a very serious problem except in a few counties of West Virginia Missouri and California

The peak year from 1923 to 1940 as shown above was 1928 but there was a previous peak in 1917–18 but at that time only 5 southern states were in the registration area The 1928 peak was probably the highest of all time to date in the United States DeKleine believes that it will never be reached again because of control measures In 1943 in the 13 states there were 1 225 deaths from pellagra or 3 2 per 100 000 a reduction of 85 7 per cent in the death rate from that of 1928 DeKleine points out that the fall in mortality beginning in 1929 has been uneven The greatest drop nearly 50 per cent from 1929 to 1932 was during the most stringent years of the depression before Federal relief started However the American Red Cross state health departments farm bureaus and other agencies had begun distributing yeast and promoting gardening in 4 states after the Mississippi floods and this extended to adjoining states so that this

program was in full swing all over the South by 1930 From 1933 on the mortality decline was much slower with a slight increase in 1936 After that year however the fall accelerated somewhat concomitantly with the general use of niacin therapy and prophylaxis DeKleine estimates that for the period studied by him there were about 50 cases of pellagra for every death from that disease whereas in an earlier period Goldberger had estimated 33 cases for every death Apparently the Federal food relief program did not influence the pellagra death rate very much

Smith and Stevens report interesting data in 590 California cases from 19 8 to 1935 They found

1 The cases were severe

2 Only 10 per cent of cases were recurrent, but recurrence was 3 times greater in dietary than in alcoholic pellagra

3 Half the cases occurred in the age group 40–59 years

4 There were twice as many male alcoholic pellagrins as female but in other classes there were more females than males

5 Native California white pellagrins were mainly alcoholics while those born in other states were mainly in the dietary deficiency and antecedent illness groups A high percentage of foreign born white patients were Italians Only 1 Oriental pellagrin was found despite a large Oriental population It is of interest that pellagra is rare in the Orient where beri beri is common

6 Half the cases developed between February and May

7 The disease was predominantly urban, in cheap rooming houses

8 There was no evidence of contact relationship among the cases

9 About two thirds of the patients died The highest death rate was in those over 50 years old and among those with dementia, diarrhea and mouth lesions 92 per cent died

In 194? Bean Spies and Blankenhorn found the incidence of pellagra in two large Ohio hospitals to be between 1 and 2 per cent of medical admissions When readmissions were included the percentage was doubled

Age — Pellagra attacks all ages Wood s records showed a child of 12 months (Fig 4) The French literature has reported cases at 3 months The disease is rare, however under 3 years In 100 cases Wood found the distribution in decades as follows

Decade	*% of Cases*
1st	7
2nd	11
3rd	24
4th	28
5th	17
6th	7
7th	4
8th	?

In 4,837 cases Merk found the following age incidence

Age in Years	% of Cases
0–5	0.9
5–15	8.3
15–30	14.7
30–40	19.0
40–50	21.0
50–60	18.7
60–70	13.1
Over 70	4.6

Cooper published an exhaustive analysis of the 712 fatal cases of pellagra reported in North Carolina in 1927. His age incidence was as follows

Age in Years	% of Cases
Under 20	6.60
20–30	15.03
30–40	20.08
40–50	16.71
50–60	16.01
60–70	13.76
Over 70	10.81
Unknown	0.98

In a group of 109 pellagrins studied by one of us (T. R. T.) in the High Point, N. C., Red Cross Pellagra Clinic in 1939 the age incidence was

Age in Years	No. of Patients	%
1–10	7	6.42
11–20	8	7.34
21–30	8	7.34
31–40	35	32.11
41–50	18	16.51
51–60	16	14.68
61–70	13	11.93
71–80	4	3.67

Among children pellagra may be trivial and go unrecognized. Wood discovered patients playing with other children who had no symptoms other than the skin lesions on their bare legs. Often the face is affected as shown in Figs. 4 and 7. Mouth symptoms may be absent or very inconspicuous. Even in the earlier pellagra studies in children, when severe diarrhea was common in adults, it was often absent or mild. However, a few fulminant cases were seen in children

in those years and they had severe diarrhea At present pellagrous diarrhea is rare in children In the early years sudden death was not infrequent in the fulminant cases especially in children

Sex — In general pellagra is much more frequent in females In 1911 the North Carolina State Board of Health reported 176 deaths from the disease of which 95 were in females and 81 in males There has been a considerable change in the ratio since then Cooper s figures showed 523 females to 189 males Our High Point Clinic figures showed an even greater disproportion 93 females (85 32 per cent) to 16 males (14 68 per cent)

Race — The morbidity is markedly greater among whites, but the mortality is higher in negroes In our High Point Clinic there were 3 colored patients to 106 white making the incidence in the negro in our series . 75 per cent Negroes make up about 10 per cent of the total population of High Point Dr M B Davis an able negro physician in this city tells us that in 9 years he has seen only 4 undoubted cases of pellagra 2 of them alcoholics in an extensive colored practice The protective action of the skin pigment against the effects of sunlight may explain this incidence The relative incidence in negroes appears to be higher in the Gulf states perhaps because of exposure to more intense sunlight than obtains in North Carolina as well as because of a higher ratio of negro to white population

Occupation — From the earliest times most of the reports have shown a higher incidence in rural areas In more recent years, however there has been an especially high incidence among operatives in cotton mill villages In the past some have attributed this to the use of out door privies both in the country and in mill villages but no proof of an infectious origin has ever been found In Cooper s series in 472 cases in which the occupation was given, he found

Occupation	*No of Cases*	%
Housewife	202	42 84
Domestic	95	20 13
Farmer	91	19 28
Day laborer	43	9 11
Mill or factory	27	5 72
Auto industry	6	1 27
Teacher	3	0 64
Newsboy blacksmith each	2	0 42
Merchant midwife pauper railroad shoemaker textile each	1	0 21

It will be noted that about 97 per cent of the cases occur under the first 5 occupational groups The case classified as textile can be properly grouped with the mill' or factory class of course

Our High Point Clinic findings as regards occupation were as follows

Occupation	*No. of Patients*	%
Housework	47	43.12
No occupation	28	25.69
Cotton mill worker	16	14.68
School child	7	6.42
W.P.A. worker	5	4.59
Hosiery mill worker	3	2.75
Laborer, midwife, N.Y.A. worker, each	1	0.91

Miscellaneous Factors. — It has been noted that pellagra occurs in the subalpine regions in Italy. In the state of North Carolina, which contains seaboard, piedmont and mountainous sections, the piedmont section is affected chiefly. In a general way this corresponds to the Italian incidence. Other factors than topographical, however, may play a part in this distribution. In North Carolina the cotton mills are located chiefly in the piedmont section, and among the families dependent upon those mills there are many errors in both diet and cookery. Such defects also are frequent among tenant farmers and certain residents in isolated villages. Among these people there is often a dearth of fresh meat except for a short period in the fall or early winter when hogs are slaughtered on the local farms. At other times fat salt pork, locally known as "fat meat," "streaked meat" or "sow belly," which is almost pure fat, is about the only meat used by many such families.

As to errors in cookery, Voegtlin noted long ago the practice among certain classes in the South of adding bicarbonate of soda to vegetables and meat to hasten cooking and produce tenderness. Voegtlin and Lake found that polyneuritis occurred in cats and dogs on an exclusive diet of lean meat heated for 3 hours at 120° C. in the presence of alkali. In addition to the above many of the families of the type mentioned rarely use yeast risen bread but subsist on corn bread or biscuits made with soda or baking powder. Until vitamin-enriched flour came into vogue, such biscuits were deficient in vitamins, and corn meal still is deficient. Pellagrins rarely give a history of the free use of dairy products. Until recently both "money crop" (cotton and tobacco) farmers and cotton mill operatives often have been too poor to purchase an adequate diet as well as too ignorant, but improving economic conditions and education are very potent factors in the recent striking reduction of pellagra.

In 1927 Goldberger and Sydenstricker reported an apparent increase in pellagra in the Mississippi flood areas, but later Dr. G. A. Wheeler stated in a personal communication to one of us (F. R. T.) that this was inconsiderable, and he attributed this fact to adequate feeding of the people by the relief forces.

pensated fairly well for nearly 6 months Then congestive failure returned, and he died in about a week

Christian has noted the appearance of pellagra in semi starved individuals after eating an adequate diet for a few days Later on the same diet the pellagra disappeared (personal communication) This has been observed in other vitamin deficiencies such as beri beri Typical avitaminotic syndromes do not develop in complete starvation, it is necessary to eat a deficient diet with a fair caloric intake to develop them

Sydenstricker Geeslin and Weaver found that increasing the carbohydrate intake and insulin in two diabetics caused glossitis and mental symptoms relieved by niacin Further increase of the carbohydrate and insulin produced a recurrence of those symptoms, which were, in turn, relieved by more niacin

Hellwig and Forman report a fatal case of pellagra associated with severe endocrine symptoms in a 38 year old female in whom it was difficult to distinguish between pellagra and Addison s disease, in which there was marked atrophy of the adrenal cortex with loss of lipoid They note that reports of endocrine disturbances in pellagrins are not uncommon and state that the clinical and anatomical findings in pellagra suggest a possible relation between niacin and the adrenal hormone They note the relations between vitamin D and the para thyroid hormone, vitamin E and the gonadal hormones and the antagonism be tween vitamin A and thyroxin as comparable phenomena

Bean, Spies and Blankenhorn classify pellagra etiologically as endemic, alcoholic and secondary They mention very numerous conditions to which they believe pellagra may be secondary, chiefly through interference with the ingestion or absorption of food Among these they list tooth extraction fracture tumor or osteomyelitis of the jaw, esophageal obstruction, peptic ulcer, old gastroen terostomy gastric carcinoma nervous indigestion, atrophic gastritis gall bladder disease chronic amebic or bacillary dysentery ulcerative colitis, tuberculous enteritis sprue hookworm habitual catharsis and chronic intestinal obstruction Many other alimentary conditions are listed by them but the present authors feel that such things as rectal incontinence are more likely to be coincidental than etiological factors The authors quoted also cite cases of pellagra following various liver diseases such as cirrhosis abscess acute yellow atrophy and hepa toma Among external agents they give a very long list of operations many of them outside the alimentary tract which might well be coincidental or precipi tated by anesthesia glucose administration, etc , and even note a case of frostbite which would certainly seem pure coincidence although it is interesting in the light of the fact that pellagrous symptoms usually disappear in cold weather The same thought of coincidence applies to their varied list of cardiovascular conditions Among endocrine disorders which might predispose to pellagra they list diabetes insipidus diabetes mellitus, thyroid disease and Addison s

disease They note that pellagra has appeared during the course of various chronic anemias As to the rôle of drugs and chemicals it would seem that only those which disturb the alimentary tract over long periods such as habituation to the opiates or substances causing liver damage would be likely to predispose to pellagra The above authors also note a number of conditions that must be purely coincidental in our opinion ranging from mosquito bite to sunstroke However one special item is of interest viz pellagra following two cases of venomous snake bite in natives of the Sudan for the authors note that Chain demonstrated that coenzyme I is inactivated by a nucleotidase from the venom of the black tiger snake Even this however seems inconclusive as one would expect any resulting metabolic disturbance to be too brief to produce pellagra unless permanent liver damage was caused by the venom or the patients had subclinical pellagra when they were bitten

J H Smith made an extraordinarily exhaustive study of the influence of solar rays on metabolism with special reference to sulfur and pellagra in the southern United States His conclusions were

1 That there are biological effects due to radiant energy is not open to question and that some of these are related to pellagra seems probable

2 An adequate supply and a normal metabolism of sulfur appear to exert a protective influence against the pathological effects of solar irradiation The evidence suggests that an inadequate supply of sulfur as cystine is an important cause of pellagra and that the abnormal metabolism of sulfur is an important feature of pellagra

3 The distribution of pellagra and the variations in its prevalence and incidence suggest that solar irradiation under certain abnormal conditions of nutrition is an important factor in the etiology of pellagra and that the reaction to solar rays not only is conditioned by the nutritive state but depends upon the state of the tissues determined by contrasts in degree and intensity of exposure during the annual cycle

D T Smith and Ruffin proved that exposure to the sun s rays of a susceptible subject who has been subsisting on a deficient diet precipitates acute manifestations of pellagra They put 15 patients on a basal pellagra producing diet A typical pellagrous dermatitis developed in 13 in 11 instances on a previously involved area but in 8 patients on previously normal skin which had been protected by clothing until exposed to sunlight during the experiment The tongue got worse in 12 diarrhea was produced in 10 nausea in 7 vomiting in 6 anorexia in 8 dementia in 4 In all 15 one or more severe constitutional symptoms developed after exposure to sunlight Neither cutaneous lesions nor general symptoms developed in any of 11 patients who were reexposed to maximal doses of sunlight following adequate treatment They noted 3 patients who developed lesions following exposure to radiant heat a red hot stove in one case a brush

fire in another and an electric stove in a third In another experiment 35 pellagrins on a deficient diet were exposed by these investigators to direct sunlight the exposure not being excessive and 15 developed symptoms, 13 cutaneous lesions and 2 constitutional symptoms without new skin lesions The first change usually noted was that the tongue became fiery red This was followed by vomiting diarrhea and sometimes, dementia Hence they warn against exposing susceptible pellagrins to the sun They raise the question as to why 20 of these 35 patients did not flare up on exposure and admit that it is hard to answer but suggest that the solution may lie in the fact that the patients, who did not develop the symptoms ate the basal diet with relish whereas the others left some of their food untouched They note also that friction as of clothing or bedclothing favors the development of skin lesions and believe that this explains such lesions on covered parts of the body

Spies was unable to show photosensitization in pellagra by exposure to the sun in Cincinnati but admitted that the rays were more or less filtered by smoke

In 1936, Sydenstricker Armstrong Derick and Kemp admitting that an extrinsic niacin deficiency is active in the production of pellagra and not denying that factors as diverse as infection seasonal influence and excessive solar radiation may play an etiologic part noted that many patients fail to improve even when substances rich in niacin were administered in great excess They treated 6 pellagrins with normal gastric juice in amounts ranging from 80 to 300 c c daily by stomach tube for from 10 to 49 days and noted practically complete disappearance of the symptoms Simple hydrochloric acid failed to produce similar improvement They concluded that normal gastric juice contains an intrinsic factor comparable to Castle s antianemic intrinsic factor, although not identical with it and that prolonged deprivation of niacin may destroy the power of some patients to produce an adequate amount of intrinsic factor Stannus also postulates an intrinsic factor

As late as 1937 Sydenstricker and Thomas stated that the definitive etiology of pellagra remains obscure, and no theory yet advanced holds in all instances or fully explains all the phenomena This is especially true of the tendency to seasonal occurrence and relapse, periodic increase and decrease and occasional epidemic prevalence Granting the effect of sunlight this must be merely a contributory factor as pellagra is relatively rare in the tropics Infection seemed an essential factor to explain the epidemic pellagra seen in the years immediately after 1906 Some years ago Spies stated that recent changes in incidence had reopened the question of the etiology of pellagra

As long ago as 1913 at the 17th International Congress of Medicine in London K Heberden Beall of Fort Worth Texas brought out some interesting points that still challenge the student of pellagra Commenting on the fact that pellagra was much more frequent in the female in America, while about equally divided

between the sexes in Europe he noted that in Europe the women worked in the fields and vineyards about as much as the men whereas in the United States the *women worked more in the home* *Moreover he showed that the incidence of* pellagra was highest in the male in the 6th decade when he is beginning to stay about the house more He further noted that in communities such as mill villages where the women work largely outside the home the incidence in the two sexes was about alike From these facts he deduced the idea that one factor in pellagra might be some thing or condition which existed in the home or around the house

A generation ago there were many stories of so-called pellagra houses as there were of cancer houses in which a series of occupants developed the disease No conclusive evidence of an infectious agent in such houses has been forthcoming however

During the years of economic depression in the nineteen thirties in High Point North Carolina there were two widely separated sections of the city in which poverty ignorance unsanitary conditions and inadequate diet were the rule Pellagra was rife in one of these sections but very few cases were reported from the other one according to Dr R A Herring City Health Officer formerly of the United States Public Health Service who was unable to account for this *difference on a purely dietary basis although it could be explained easily on a* dietary infectious basis

In 1923 Jobling and Arnold pointed out that the radical changes in incidence did not seem to be associated with comparable shifts in the diet of the population involved *The work of Siler Garrison and McNeal (Thompson McFadden Pellagra* Commission) has been noted in the section on History

Sydenstricker states that an uncomplicated single avitaminosis is unlikely in a human being especially a deficiency of a single member of the B group Members *of this group commonly occur together so that a deficiency of one usually* means a deficiency of others In pellagra in addition to the specific niacin deficiency riboflavin and thiamin also may be inadequate in the ration Hansen Pruss on the other hand says that it is surprising that there is so little overlapping *of deficiency diseases* In 66 sprue patients in the Duke Hospital Clinic *no instance* of pellagra beri beri or scurvy was found One patient was observed however who recovered from a sprue cachexia on repeated parenteral liver extract and diet who 17 months later showed typical pellagra that cleared up on niacin However while receiving the refined liver extract he developed *pyloric obstruction from* a stenosing ulcer which lessened while he was taking the niacin Hansen Pruss believes that refined liver extract such as is usually given in pernicious anemia does not contain a sufficient amount of niacin to be employed in treating pellagra

One of the strongest arguments against the pure niacin-deficiency *theory of* etiology is the fact that a number of pellagrins have recovered while kept on an extremely deficient pellagra producing diet without other treatment The

20 patients of Ruffin and Smith, already cited, were definite pellagrins who recovered on such a diet even though given exposure to sunlight However, lessened metabolism due to bed rest may explain this Spies reported 4 similar cases in a hospital with little exposure to sunlight Later he reported 10 additional cases with no nervous lesions while on a still more restricted diet, 8 of whom tolerated the diet for some time and whose skin lesions cleared up during that time The stomatitis disappeared in one of these 8 and got worse in 3 In several other patients, nervous lesions got worse, while skin lesions cleared up on the deficient diet As will be seen in the section on Treatment, Ruffin and Smith in attempting to evaluate the potency of various therapeutic agents put 107 pellagrins on their basic 'pellagra producing" diet and 30 of them recovered on bed rest without other treatment Only those who showed no spontaneous improvement, were given the various preparations on trial

Greenfield and Holmes reported a case of pellagra in a 5 year old boy who had plenty of fresh vegetables milk and butter "with perhaps an excess of the latter , as his parents were farmers Dr O L Miller formerly Chief of the North Carolina State Orthopedic Hospital cited the case of a patient who was known to have eaten a generous balanced diet containing plenty of meat and milk who developed pellagra apparently for the first time after 6 months in the hospital (personal communication)

Remington discusses a number of facts in connection with pellagra which are hard to interpret in the light of our present knowledge of deficiency diseases Commenting on DeKleine s statistics, which have been mentioned in the section on Distribution and Incidence, he rejects the explanation that the striking reduction in incidence between 1928 and 1940 can be accounted for by the widespread use of brewers yeast, the promotion of gardening or the introduction of niacin therapy and education and says that a closer study of the mortality statistics broken down as to sex race and age together with such collateral information as the year to-year purchasing power, incidence rates where they are sufficiently reliable and data as to the amount of dry yeast distributed reveals information not in accord with DeKleine s conclusions yet without in most cases yielding any clear cut substitute for them Up until the economic depression that began late in 1929 we were told constantly that pellagra was a disease of poverty yet as poverty increased pellagra declined It is interesting to note that it declined faster in negroes than in whites Federal distribution of money or food through various relief agencies was not accompanied by any striking reduction in incidence Indeed there was a slight increase during the years when it was operative

The frequency of fulminant cases when pellagra first appears in a community in contrast to their rarity after the disease has become endemic suggests, perhaps more strongly than any other factor the possibility of some infectious agent s playing an etiological part Moreover, when the disease first broke out in epi

demic form in the southern United States it affected the very poor least exclusively and tended to involve all classes to a greater degree than after it became well entrenched However our findings in the High Point Pellagra Clinic in 1939 showed nothing to support the idea that pellagra is spread by unsanitary excreta disposal or lack of screening In our 109 cases we found these factors as follows based we must admit not on observation in the homes but on statements made by the patients in response to questions on these matters

Excreta Disposal	*No of Cases*	%
Water borne sewage plumbing good	68	62 39
Water borne sewage plumbing defective	5	4 59
Sanitary privy	16	14 68
Unsanitary privy	13	11 92
Indefinite	7	6 51

Screening	*No of Cases*	%
Good	50	45 87
Fair	11	10 09
Poor	18	16 51
None	17	15 60
Unspecified	14	12 84

There is an error in this last table of 1 case too many but as we do not know from which group it should be subtracted we let it stand the original case records being no longer available since the permanent closing of the clinic due to the reduction of cases in the community It does not affect our conclusions

A very interesting point should be considered regarding the fulminant cases seen so often in former years and so very seldom now In those days sanitation and hygiene were not what they are now and all sorts of non pellagrous enteritides dysenteries etc were more frequent It will be seen in the section on Chemistry that niacin accelerates the growth of dysentery bacilli The original non pellagrous diarrhea would interfere with the absorption of the little niacin in the deficient diet and if a diet rich in niacin or yeast was given a bacillary dysentery might get worse and cause the patient s death Greenfield and Holmes have cited an actual case of pellagra in which the diarrhea appeared to be due to *Shigella dysenteriae* In recent years with improved sanitation and hygiene diarrhea once considered almost a requisite for the diagnosis of pellagra has largely disappeared and constipation is frequent as will be shown in the section on Symptoms and Clinical Findings

Seale Harris Jr has expressed his belief that pellagra is not due to any specific infection but that a variety of infections which predispose to liver insufficiency may be factors in the genesis of the disease

It is interesting to note that several authorities are still uncertain as to whether

an infectious factor can be excluded entirely, especially in the etiology of fulminant cases A letter from Professor Kenneth M Lynch of the Medical College of the State of South Carolina dated October 10, 1945 says "I still feel that the dietary theory is apparently inadequate to explain all of the phenomena observed as you have stated" Another letter from Dr James S McLester of Birmingham Alabama dated October 17, 1945, says "I still feel that there are several factors, possibly all of them nutritional, in the production of pellagra but I am not entirely sure there is no other factor Whether there is in addition a non specific infectious factor, it is hard to say I have no objection to your quoting me as saying that much of the pellagra we saw 25 years ago suggested the existence of such a factor Still another from Professor William B Porter of the Medical College of Virginia says in part "I have read your letter with much interest and frankly with much satisfaction The problem of pellagra is still an unsolved one and anyone who has given the question consideration realizes this fact You are arousing interest and further thought in the matter which will not allow investigators to settle on niacin deficiency as the sole factor concerned in this very complicated disease Furthermore I think the most convincing factor as far as we are concerned is what we reported in our study on the heart in pellagra, namely that in not a single instance have we noted a large heart such as occurs in B_1 deficiency with beriberi heart with our findings in the heart in pellagra All the above letters were addressed to the senior author in reply to letters from him

Another communication of great interest is from Dr Julian M Ruffin of Duke University written a few weeks after his return from a special nutritional study in Germany since the close of World War II He was working in the American Zone of Occupation and says that he can state without fear of contradiction that there was no pellagra in that area He saw none himself in 5 000 examinations of civilians nor was any reported by other nutrition teams He talked with men who had made similar surveys in Italy and Greece and they reported no pellagra in those countries

Alcoholic pellagra" has been mentioned This is the form usually seen in the northern United States where endemic pellagra is rare Alcohol per se does not cause pellagra but the usual loss of appetite with resulting inadequate diet in chronic alcoholism may be an important factor The experiments of Klauder and Winkelmann who permitted old alcoholics to drink large amounts of alcohol on the condition that they eat the generous diet provided them and watched them recover from their pellagra despite the continued alcohol seem decisive

Blankenhorn and Spies note that the oral lesions of chronic alcoholism are very similar to those in pellagra and clear up dramatically on yeast liver extract or wheat germ In their series of over 200 alcoholics 60 per cent had such oral lesions and they precede the more fully developed alcoholic pellagra The au

thors believe that the peripheral neuritis seen so often with alcoholic pellagra is no part of the pellagra but due to a thiamin deficiency i e it is the ordinary *form of so-called alcoholic neuritis Most observers agree with this*

Jellinek states that there is still considerable question as to the exact role of alcohol in alcoholic' pellagra He notes that the inebriate who subsists for several weeks on liquor alone is unique in his ability to obtain a diet high in calories yet completely free of vitamins He also points out that the alcoholic is especially subject to infections and often has acute delirious episodes that increase his metabolic needs considerably and these factors may precipitate a clinical vitamin deficiency He notes further that many alcoholics have chronic changes in the gastrointestinal tract which may interfere with efficient absorption and utilization of niacin although this factor seems largely negated by the fact that niacin absorption in alcoholics with severe gastric symptoms usually is very *rapid judged by the prompt appearance of the vasomotor reaction* Jellinek considers that interference with the utilization of vitamins by hepatic and endocrine disorders is not certainly established He cites Boggs and Padget as thinking that alcohol either destroys niacin in the gastrointestinal tract or causes changes in the tract that prevent its assimilation but then quotes Jadassohn as saying that the combination of inebriety and undernourishment cannot fully explain the onset of pellagra for if it could alcoholic pellagra would be much more frequent than it is

Inasmuch as an exclusive liquor diet is free of all vitamins we must ask why one patient develops polyneuritis another pellagra but practically none rickets scurvy etc and most alcoholics do not develop specific vitamin deficiency states at all The answer to this so far as pellagra is concerned is suggested in the section on Chemistry

As noted in the section on History several recent observers have brought back *the subject of the part played by maize in the production of pellagra They find* that a basic pellagra producing diet containing maize seems to show an antagonism to niacin The addition of casein to the diet seems to overcome this antagonism

Dann in a personal communication calls attention to the fact that Krehl Teply Sarma and Elvehjem added lysine and tryptophane to the basic diet as casein is rich in these amino acids whereas corn is poor in them Lysine had no action but 0 05 per cent of 1(-) tryptophane overcame the inhibition of growth produced by corn in experimental rats as did niacin The interchangeability of tryptophane and niacin may be due to an effect of the tryptophane on the intestinal flora favoring the growth of organisms which synthesize niacin the action of niacin being direct that of tryptophane indirect

In North Carolina from 1923 to 1929 an era of prosperity *deaths from pellagra* increased about 2½ times as fast as the population yet during this period a great state highway system was built and along with it went a very marked improve

ment in the public school system with the erection of large consolidated schools with free bus transportation Home economics was taught in these schools In addition, county demonstration agents in home economics were at work, womens clubs were multiplying throughout the state and the people knew better how to eat properly and had more money to buy food than ever before, yet the pellagra death rate increased by leaps and bounds In 1930, there was a slight increase in deaths from pellagra over 1929 but in 1931 a drop of over 31 per cent in the deaths as compared with 1930, and in 1932 a further drop of over 33 per cent as compared with 1931 yet these last two years, especially 1932 were at the very depth of the economic depression During the prolonged depression after 1932 the general trend continued slowly downward with slight fluctuations

This is precisely the opposite of what one would expect with a disease due solely to a dietary deficiency The incidence was greatest when the people could afford better food, and much less, when many were suffering from a food shortage due to poverty Governmental feeding of the people on a large scale did not become operative until 1933 so this cannot explain the very sharp drop in 1931 and 1932 The pure dietary school of thought argues that the depression stopped the exclusive raising of cotton and tobacco and made the farmer raise more food and that loss of industrial jobs put many persons back on the land for a living and that the state wide propaganda urging everyone to own a cow and a garden was responsible for the drop in pellagra incidence These arguments seem highly inconclusive to some however including the senior author for very many were unable to own a garden or a cow or to go back on the land yet the most striking reduction in pellagra that has been noted in recent years occurred under these very circumstances

Are hereditary or familial factors significant in pellagra? Bloom recognized "hereditary juvenile pellagra " but his criteria of heredity seem rather vague In Vol I Chap XII of this work Davenport writes "As for vitamin insufficiencies a study that was made at the Eugenics Record Office of the incidence of pellagra in Spartanburg S C, showed very clearly that the disease ran a virulent course only in certain families and indeed in cases where effects followed these were of different type in different families There were families characterized principally by dermal symptoms others by intestinal symptoms, others by symptoms of the central nervous system Similarly the ability to resist the insufficiency of particular vitamins seems to vary in different individuals, and this difference probably has a genetic basis "

The senior author knows of 5 siblings all living in different places with almost no contact with one another all of whom developed pellagra

To sum up the question of etiology therefore we may say that the most important single factor is a niacin deficiency due to a deficient diet or to inadequate absorption storage or utilization of that substance Exposure to certain types

of radiant energy especially sunlight may precipitate symptoms Lack of an intrinsic factor in the gastric juice is strongly suspected as playing some part Sulfur metabolism may have some significance Finally at least so far as the epidemic fulminant cases are concerned some unknown infectious factor specific or non specific may play a part In addition to this corn products seem to contain a substance or substances that increase the niacin requirements of the body perhaps by inhibiting the growth of niacin producing bacteria in the alimentary tract Other vitamin deficiencies notably of thiamin and riboflavin frequently are associated with pellagra but are associated conditions rather than integral features of pellagra itself

CHEMISTRY

Niacin is a component of coenzymes and codehydrogenases without which many known dehydrogenases are inactive *It is a chemically active fraction of* coenzymes 1 and 2 which are essential for carbohydrate metabolism Stannus in 1940 and Sydenstricker in 1941 felt that failure of this action resulted in the signs and symptoms which we recognize as pellagra It is thought however that the degree and rapidity of niacin depletion may alter the clinical picture Stannus suggests that particularly in alcoholic pellagra the dehydrogenase which oxidizes alcohol requires coenzymes 1 and all the other links of the chain He feels that as a competitor for these substances it causes interference with the dehydrogenase systems of the body and that similar results may be produced by other competitors such as the glucose dehydrogenase increased activity in the presence of reduced capacity for oxidation reduction processes infection work fever pregnancy thyrotoxicosis or possibly a diet containing an inhibitory action on cellular respiration present in corn and bearing the same relation as does alcohol

It has been suggested that excessive formation of porphyrins with chronic porphyrinemia or sensitization might explain the relation between dermatitis and exposure to the sun Many reports have been made on porphyrinuria of pellagrins The chromogenic substance called porphyrin by Beckh Ellinger and Spies was found by them in the urines of 19 pellagrins 14 of whom were alcoholics These workers felt that the porphyrin output was related to the severity of the cutaneous lesions and returned to normal with the regression of the disease This report of increased prophyrin excretion is of interest in view of the work of Smith and Ruffin *in which they proved the relation of exposure to sun in the* development of the pellagra dermatitis and the known photosensitivity in congenital porphyria

Kark showed that while alcoholic pellagrins *occasionally excrete increased* porphyrin it is not a constant finding and is unrelated to exposure to sun or to dermatitis Further studies indicated that porphyrinuria occurs in many pathological conditions and is largely an indication of co-existing hepatic dysfunction

TABLE II

MULTIPLE DEFICIENCIES

	B COMPLEX						
Number of subnormal values per patient	0	1	2	3	4		
Number of patients	2		8	13	1		
	B COMPLEX PLUS A CAROTENE AND C						
Number of subnormal value per patient	0	1	2	3	4	5	6
Number of patients	1	1	0	15	7	1	1

Sydenstricker and others have pointed out that the B complex occurs together in nature as well as having closely related physiological functions, therefore, inadequate intake or utilization is apt to affect the entire group No naturally selected diet is apt to be deficient in a single vitamin He felt that pellagra probably represented a group B deficiency in which niacin deficiency was predominant The work of Ruffin Cayer and Perlzweig appears to justify this thesis They formed the following conclusions on the basis of their study

1 The results obtained from the laboratory determinations of B complex vitamin levels in general paralleled the clinical evidence of a deficiency state

2 In a group of patients classified clinically as having a B complex deficiency the levels of niacin, thiamin and riboflavin were significantly lower than those of a normal control group

3 Among patients showing signs of a B complex deficiency the laboratory data indicated the prevalence of multiple deficiencies

These workers later showed that, in the same group of patients studied a *niacin deficiency was a far more frequent cause than was riboflavin* not only of glossitis but also of cheilosis

PATHOLOGY

The pathological changes described in pellagra are varied in extent and character and few can be regarded as distinctive The findings in many instances vary with the chronicity of the disorder The acute fulminating type formerly seen so frequently in the southern states often showed no definite pathological lesions except for the cutaneous manifestations This was true even where sudden death intervened Degenerative changes in the spinal cord, however have been observed in cases of only a few weeks duration

The dermatitis itself may not be present always When it is its appearance is

characteristic Symmetrical lesions may appear on any portion of the body and usually are demarcated sharply from the areas of healthy skin The dermatitis usually begins as an erythema resembling sunburn Vesicles and bullae may form followed by desquamation In the absence of secondary infection the underlying tissue becomes red and thickened and later is pigmented a reddish brown The skin changes may not parallel the severity of the disease and asymmetrical cutaneous lesions may occur In such cases it is thought that local anoxia or increased metabolic needs are responsible

The cutaneous lesions vary with the progressive stages of the disease The skin may become lax and wrinkled due to separation of the epidermis from the corium The later lesions become rough pigmented thin shiny and atrophic Denton described the following histological picture Small circular areas of rarefaction of the corium appear The vessels are dilated lined with large endothelial cells many with mitotic figures The collagenous binding between the epidermis and the corium is destroyed and vesicles appear The primary foci coalesce and cause extensive separation of the epidermis Telangiectases develop from capillary and pre capillary vessels by distention In late lesions the deep vessels show marked thickening and sub-endothelial proliferation of the intima The small cutaneous nerves show no evidence of damage Bacterial invasion results in thrombus formation and necrosis Repair is imperfect and a thin layer of epithelium regenerates Many pathologists report hyperkeratosis Raffini studied the skin in 3 cases and found the horny layer to be hypertrophic with hyperplasia of the rete Malpighii and sclerosis of the vessels of the papilli and deeper layers and also of the corium Raymond emphasized atrophy as the inevitable result of repetitions of the pellagrous process Hemorrhagic skin lesions also have been observed It must be remembered that maceration weeping and secondary infection may alter the appearance of the skin to a marked degree Such cases when neglected present a very loathsome picture

Ulcerations in the mouth and tongue are an early and conspicuous part in the symptomatology and pathology in pellagra There is marked hyperemia and erythema of the mucous membrane of the entire oral cavity The tongue may become fissured and the edges may show papillary atrophy Ulceration may occur also on the margins or beneath the tongue The ulcers often become invaded secondarily by pyogens and Vincent s organisms Later the mucous membranes may appear brownish red with grayish areas due to necrosis of epithelium The salivary glands are enlarged and sensitive to pressure This change often is accompanied by the distressing salivation so frequently noted in severe cases In some instances esophagitis is marked The color of the esophagitis is that of the mucous membrane of the mouth The examination by esophagoscopy reveals chronic inflammatory change with secondary ulceration The microscopic picture shows erosion with false membrane formation and degeneration of epithelial

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FIGURE 1 Intestine of pellagra magnified 91 times Ulcer of mucosa inversion of edge mononuclear infiltration fibrosis and arteriolar sclerosis at base in submucosa Courtesy of Kenneth M Lynch Medical College of the State of South Carolina Charleston S C

cells with dilated vessels. Changes in the stomach are indefinite. Occasionally gastritis with pseudomembranous inflammation is found. Thinning of the wall with atrophy of the glandular tissue has been described also, and fibrotic changes may occur in chronic cases. The small intestine in the autopsies described by Denton was strikingly dark in color. There was a decrease in subserous fat and engorgement of intestinal walls. Several cases showed gross enteritis, most marked in the terminal ileum. There was no change in the lymph nodes.

Professor Kenneth M. Lynch of Charleston, South Carolina, reported in 1916 and again in 1929 before the American Society of Tropical Medicine on changes in the pellagrous intestine which he considered to be characteristic. He believes it is even possible to make a post mortem diagnosis of pellagra from the intestinal findings in some cases in which it has been clinically impossible, as for example in the absence of a typical dermatitis. Among other things, he notes the following points:

1. The inflammation of the intestine usually is limited to the colon, extending into the terminal part of the ileum in severe cases. The cecum, sigmoid and rectum are involved most extensively and in mild cases may be the only part of the colon affected.

2. The wall of the involved intestine is thickened and congested and the peritoneal surface may be fibrous. The surface of the mucosa usually is rather flattened with decreased plication. It may be of a leathery toughness and have a bronzed tint. Gross ulcers occur only in aggravated cases, and then they are superficial, irregular and granular without elevated edges. They may be quite extensive. Usually when they occur they are limited to the cecum but at times extend over the ileocecal valve. Deep ulceration with perforation was noted in only one case. Lynch considers the distribution of the process, the flattened, deep red bronzed or thickened mucosa and the shallow irregular mucosal ulcers as characteristic.

Microscopically (Figs. 1, 2 and 3) Lynch finds equally characteristic changes, among which he notes:

1. In the mucosa, hyperemia, degeneration and desquamation of surface epithelium, increase in interglandular mononuclear and connective tissue cells, and cystic dilation of the mucous glands, which appear to be blocked at the mouth or neck and are distended by an accumulation of degenerated epithelium, acidophilic granular detritis and possibly a few leucocytes preserved or disintegrated. The cells lining these cystic glands are flattened markedly. They usually have a deeply acidophilic hyaline cytoplasm, the cell borders appear fused, the nuclei sparse and some are large and hyperchromatic. At times two or more layers of hyalinized epithelium may be flattened against the wall, suggesting epithelial proliferation. The number and size of these distended glands vary with the grade of inflammation. They are especially marked in the cecum.

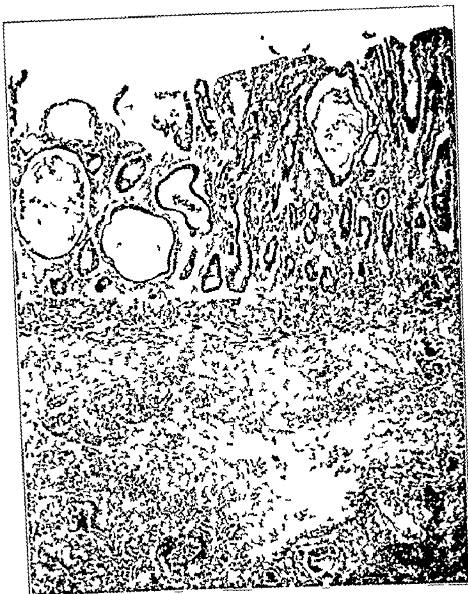


FIGURE 3 Intestine of pellagra magnified 110 diameters Cystic glands of mucosa with flattening and atrophy of lining epithelium Nuclei of some of these flattened cells large General fibrous mononucleosis with involvement of nerve centers in submucosa Courtesy of Kenneth M Lynch Medical College of the State of South Carolina Charleston S C



FIGURE 2 Intestine of pellagra magnified 110 times Cystic mucosal glands containing desquamated epithelium mucus and one with leucocytes Atrophy of epithelium of mouths of cystic glands Fibrosis and some mononucleosis with arteriolar sclerosis and congestion of a vein in submucosa Courtesy of Kenneth M Lynch Medical College of the State of South Carolina Charleston S C

Important pathological changes are found often in the nervous system The literature on this subject is voluminous There is a certain unanimity in the reports despite minor variations in observation S A Kinnier Wilson made an important contribution in his study of 13 cases some of which were South African cases collected by Hugh S Stannus A few were British cases Peripheral nerve changes were constant and advanced in the nerves examined sciatics popliteals medians and ulnars Degeneration of the myelin sheaths occurred irregularly Emphasis was placed on the presence of granules of Reich *in markedly increased amounts and there was great increase in the cells containing* granules In the presence of degeneration immense quantities were found lying in the meshes of honeycombed and imbricated myelin in the neurokeratin network altogether away from the Schwann cells This is taken to indicate abnormal metabolic and toxic changes in peripheral nerves Reference is made to findings by Mario Zalla of granules in quantities in the peripheral nerves in pellagra The presence of Ehrlich s mast cells is regarded as an indication of abnormality of the peripheral nervous system and reaction to toxic invasion The posterior roots of the spinal nerves presented the same changes *that were seen in the sciatic nerves diffuse degeneration both parenchymatous* and interstitial The cells of the posterior root ganglia showed subacute degeneration with eccentricity of the nuclei and central chromatolysis with pigmentary degeneration in many instances Some cells were swollen and some atrophied but there was no indication of inflammatory reaction In accord with the observation of many others Clarke s column was the most severely affected portion of the spinal cord manifesting all stages of chromatolysis As a rule there occurred typical subacute cell degeneration with perinuclear chromatolysis displacement of the nucleus and swelling of the contour of the cell passing finally *into pigmentary degeneration and atrophy In many sections he was unable to* find a single normal cell in Clarke s column The cells of the intermediolateral tract showed diffuse degeneration and atrophy The anterior horn cells were affected sometimes but not constantly He found lesions in the white matter more noticeable in the posterior column cells than elsewhere The columns of Goll and Burdach were affected in varying degree the columns of Goll more than of Burdach The changes in both tracts were diffuse In his experience degeneration of the posterior tracts was more frequent than that of the lateral tracts but in no instance was the process confined to the limit of any system *The spinocerebellar paths may show diffuse and scattered degeneration which is* not limited strictly to this portion The cord lesions were regarded as pseudosystematized mainly in the posterior and lateral columns resembling a combined sclerosis but as the lesions were not confined to anatomical paths the condition can not be regarded as a systematized tract degeneration Marginal degeneration of the cord occurs and degenerated fibers are found indiscriminantly over the

2 The submucosa shows marked congestion the veins being especially distended with blood There is a progressive growth of fibrous tissue and a diffuse infiltration by large mononuclear cells, lymphocytes and plasma cells In severe cases the tissue spaces and lymphatics may be choked with these cells The muscle coats and serosa show a similar infiltration and fibrosis This produces the thickening of the wall noted grossly

3 When ulcers occur usually they are limited to the mucosa Cystic mucus glands often are conspicuous in the edges of the ulcer These edges are slightly undermined with the epithelium of the border inverted Unusually deep ulcers may show necrosis of the border tissue, and polymorphonuclear neutrophiles are present along with the other cells

4 There is nothing characteristic in the lymphoid tissue except for mild lymphadenitis

Therefore the characteristic findings in long standing cases Lynch concludes are fibrosis and atrophy of the mucosa and submucosa with conspicuous hyalin fibrosis of the latter He has noted also sclerosis of the small blood vessels supplying the area involved out of proportion to the general arteriosclerosis In addition to this he has described degeneration and atrophy of the nerve ganglia in the wall of the involved bowel especially in long standing cases and he offers this as an explanation of the absence of diarrhea in many such cases

Dr J B Bullitt Professor of Pathology at the University of North Carolina, believes that degeneration of the ganglia is a post mortem change (personal communication)

Denton also describes the changes in the colon as being constant and specific He found the epithelium intact except in small areas where there was microscopic necrosis with a fibrinous covering containing bacteria and degenerating cells He also notes numerous cysts forming in dilating glands lined with the remnants of epithelial cells Some of these were filled with mucus The stroma is hyperplastic and contains short blunt vascular loops There was a marked increase in cells about the small vessels and lacteals He states that chromatolysis in ganglion cells is not found regularly Mitosis in cells is frequent He notes as the most striking feature the change in surface epithelium and peculiar dilatation of the blood vessels of the submucosa

Harris quotes Sydenstricker as finding liver changes in 92 per cent of 440 cases Gillman and Gillman report a study of .o children suffering from severe pellagra on whom repeated liver biopsies were done The outstanding feature of these livers was the great amount of fat scattered throughout in the form of pale globules filling the cells There was no necrosis or hemorrhage The livers were remarkably avascular the sinusoids closed, and it was difficult to identify any but the larger branches of the hepatic veins In many cells large vacuoles were present

to develop characteristic pellagrous lesions Usually if niacin is administered he improves rapidly Gastric analysis at this time may show normal acidity or hypochlorhydria Excess of mucus is frequent Vomiting is infrequent A brief trivial diarrhea may occur often it is absent Anorexia and insomnia are common These rather nondescript symptoms may exist for a part of one or two years before a more complete picture develops if it develops at all It is of interest to note that pellagra practically never appears first in the winter months at least in localities where the winters are cool enough to have frost although as noted in the section on Distribution and Incidence a number of California cases occur in February

Skin Manifestations

Although gastrointestinal symptoms often precede those in the skin the latter are the most important symptoms of pellagra from the standpoint of diagnosis so are discussed first (Figs 4 to 12) The extent of the skin surface involved is no indication of the severity of the disease While usually fairly extensive in very severe cases they may be so insignificant as to require careful search The dermatitis is almost always symmetrical This is probably due to the symmetry of the exposure of the various parts of the body to either sunlight or the friction of clothing D T Smith has produced asymmetrical lesions by exposing one arm to sunlight while keeping the other covered etc In the spontaneously occurring disease if an asymmetrical lesion appears it is likely to be followed soon by a corresponding lesion on the other side Wood saw a small patch of dermatitis appear at the outer canthus of one eye and marked a similar area outside the other eye and watched a symmetrical lesion fill the marked area in a few days Openings have been made in the clothing of pellagrins and skin lesions corresponding to the patterns of the openings have appeared The most usual location of the dermatitis is on the backs of the hands (Figs 5 and 7) The hands were so affected in 97 per cent of Wood s patients A small area over the metacarpal region may be affected or the knuckles may appear chapped The whole *posterior aspect of the hands and fingers to the nails may be involved The latter* seldom are damaged although Roberts notes that they may fail to receive proper nourishment and drop off Neither Wood nor the present authors ever saw pellagrous involvement of the nails Not infrequently the dermatitis extends above the hands It may involve all of the forearms like a gauntlet (Figs 5 and 7) Often the flexor surfaces of the forearm escape except for the lowest 2 or 3 inches roughly corresponding to the location of the pronator quadratus muscle (Fig 9) while the extensor surfaces are affected to the elbow or even above Symmetrical involvement of the arms is shown in Fig 5 In the High Point Pellagra Clinic the upper extremities showed skin lesions in 79 82 per cent of the cases Next

whole transverse section, endogenous and exogenous fibers alike degenerating There is marked resemblance to subacute combined degeneration This view is based on myelin disintegration diffuse and unsystematized and the presence of compound granular corpuscles together with absence of inflammatory reaction around the blood vessels

Greenfield also describes chromatolytic changes of varying degree He describes the greatest change in the anterior horn cells of the spinal cord and the cells of the craniomotor nerves He describes the condition in the nervous system as one of neuronal degeneration The basal ganglia and motor cortex may be involved severely and diffusely The degeneration in the motor cortex is one of the most common changes in pellagra and is described by Adolf Meyer as "central neuritis' Pearson in 1928 described 9 cases, all showing this central neuritis H A Cotton studied the brain and cord of one of Wood's cases and confirmed his beliefs that there was a marked similarity to the neuritis described by Meyer Grossly there may be atrophy of the cerebrum Langsworth states that the Italian pathologists report changes in the meninges consisting of thickening and opacity of the piaarachnoid in practically all of their cases

Numerous non specific changes have been observed in pellagra There may be a wasting of adipose and muscle tissue, although the remaining subcutaneous tissue and fat are apt to appear normal There are no focal hemorrhages The respiratory system is negative except for hypostatic changes in the lungs The genitourinary system occasionally shows mild degenerative changes in the tubules but no lesions directly referable to pellagra The spleen is small In Denton's report of 12 cases no lesions were demonstrated in the adrenals, thyroid or pancreas The heart is uniformly small due to diminution in size of the muscle fibers The vessels of the heart are unchanged The degree of malnutrition is in proportion to the duration of the disease Pellagrins are prone to have tuberculosis, amebiasis and other intestinal parasites and protozoa, which in many instances may cause considerable confusion as well as altering the course of pellagra to a marked extent

Symptoms and Clinical Findings

There is a prodromal period in pellagra which is as truly a part of the disease as is the eruptive stage Indeed at the present time when frank pellagra is much less frequent than formerly many cases do not progress beyond this stage and must be regarded as niacin deficiency states of mild degree rather than full blown pellagra Some call this 'subclinical pellagra' The symptoms and signs at this stage are vague and indefinite and without a history of previous well developed attacks may be difficult or impossible to explain satisfactorily Such cases are often labeled psychoneurosis ', and the patient may or may not go on



Fig 5 —Showing the skin gauntlet extending from the finger nails to the elbows The lesions of the arms present the lamellated appearance (Courtesy of the Illinois State Board of Health Dr J A Eagan Secretary)

in frequency with regard to the dermatitis come the lower extremities (Figs 7, 8, 10 and 11) These were affected in 60 per cent of our cases in High Point Those who are barefooted are especially liable to lesions on the feet When shoes are



FIG 4 — A negro child of twelve months Lesions of the backs of the hand and the pellagrous mask (Courtesy of the late Dr Edward Jenner Wood)

worn without hosiery the dermatitis of the feet and legs may stop at the shoe level In Wood s series the feet were involved in 16 per cent Third in frequency

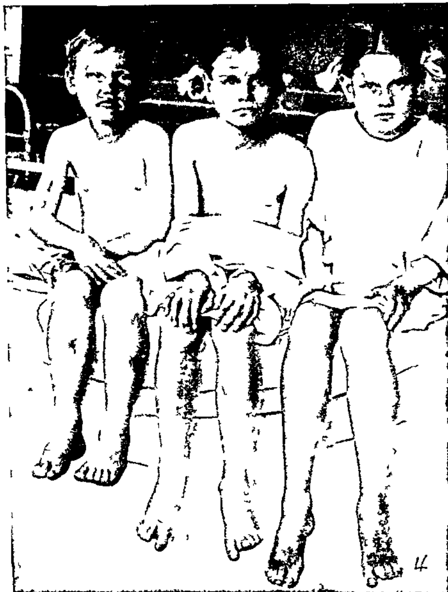


FIG 7 — Shows three children of one family with skin lesions of the feet and legs Note the pellagrous marks especially of the boy Note also the hands and forearms. (Courtesy of the late Dr Edward Jenner Wood)

of involvement come the face and neck, the so called pellagra mask, with Casal's collar Wood reported involvement of the face in 27 per cent of his cases and of the neck in 28 5 per cent (Figs 4 and 7) In High Point we had involvement of the face and neck in 31 per cent of our patients Fourth in frequency but far less common than the sites already mentioned is the back, especially over the spinous processes of some of the vertebrae (Fig 11) In our High Point series the back was involved in 5 per cent We have seen such involvement in the form of a few small patches over 2 or 3 spinous processes as the only skin involvement in a patient Involvement of two or more parts of the body, especially of the hands feet and face is more common Figs 9 10 and 11 show the same patient Other areas than those mentioned are affected only occasionally Scrotal involve



Fig 6 — Shows the symmetrical skin lesions about the vulva The patient is a mulatto. (Courtesy of the late Dr Edward Jenner Wood)

ment has been mentioned in connection with Goldberger's work and is noted not infrequently when searched for The same applies to lesions about the vulva (Fig 6) In our High Point series involvement of the abdomen was noted in 1 case and of the chest in another

Some cases show a bullous or vesicular eruption with subsequent marked weeping and desquamation In recent years this has been much less frequent than in the more acute and fulminant cases of 30 years ago Rarely the lesions may be curiously lamellated as on the upper arms in Fig 5 Wood attributed this



Fig 9 — Shows a woman with skin lesions on the lower anterior surfaces of the forearms and the tips of the elbows (Courtesy of the late Dr Edward Jenner Wood)

to multiple attacks of erythema occurring so closely together that one attack could not heal before another developed

Bennett Spies and Vilter noted that the skin lesions in different parts of the body are often in different phases simultaneously such as early erythema on the

Pellagra universalis is mentioned in the literature This is rare The present authors have never seen a case in which practically the entire skin surface was involved

The classical skin lesion appears first as an erythematous dermatitis which may be confused with sunburn by the unwary Later, there usually is scaling fissuring and a brownish pigmentation In the negro the pigmentation may be

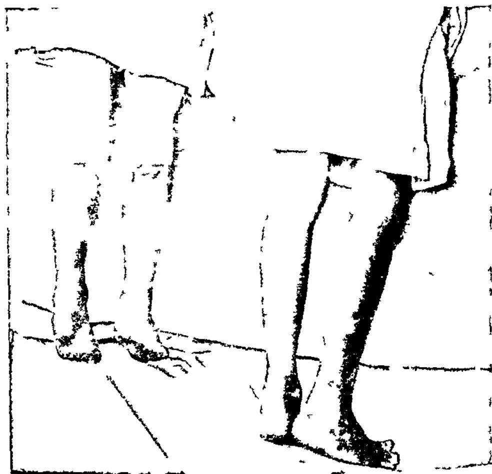


Fig 8 — Two of the children of Fig 7 Note the lesions of the legs with the sharp symmetrical lines of demarcation (Courtesy of the late Dr Edward Jenner Wood)

almost coal black in some areas This is less intense in the mulatto and a true black pigmentation is unusual in the Caucasian Wood has pointed out that the contrast between the pigmented and non pigmented areas is especially marked in the Egyptian more so than in the North American white or negro which possibly may be due to peculiar rays or intensity in the Egyptian sunlight '

arms with desquamation and pigmentation on the legs whether the patient works in the fields or is confined to bed They also cite 5 cases of unilateral dermatitis associated with asymmetrical varicose veins 5 cases of asymmetrical dermatitis influenced by trauma pressure and irritation 2 cases with unilateral dermatitis in infected extremities and 1 case showing less involvement of a paralyzed arm than its unparalyzed fellow They also report asymmetrical eruptions without obvious cause in 2 cases Sunlight was not a factor in the asymmetry in any of these cases

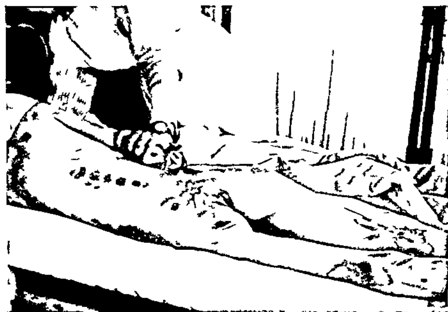


FIG 11 — Same patient as shown in Figs 9 and 10 Note lesions over the posterior aspects of the knees, tubera ischiorum posterior superior spines of the ilia and fine spots along the spine (Courtesy of the late Dr Edward Jenner Wood)

Smith Ruffin and Smith of Duke University have emphasized the specificity of another skin lesion frequently seen in pellagra which is entirely distinct from the dermatitis or erythema This is the development of horny concretions in the orifices of the sebaceous glands of the face Fig 12 made from a photograph presented by Dr David T Smith shows such lesions They tend to appear with the dermatitis and disappear with it on adequate treatment

Sullivan cites a case in which after the usual pellagrous symptoms had subsided on dietary treatment bilateral symmetrical trophic ulcers appeared on the feet healing in 8 weeks on protective and antipruritic ointments and other medi



FIG 10 — Same patient as shown in Fig 6 The lesion is well shown over the knees, about the external malleoli a spot over the first tarso metatarsal joints and slight over the toes. (Courtesy of the la e Dr Edward Jenner Wood)

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FIG 11 — Same patient as shown in Figs 9 and 10 Note lesions over the posterior aspects of the knees tubera ischiorum posterior superior spines of the ilia and fine spots along the spine (Courtesy of the late Dr Edward Jenner Wood)

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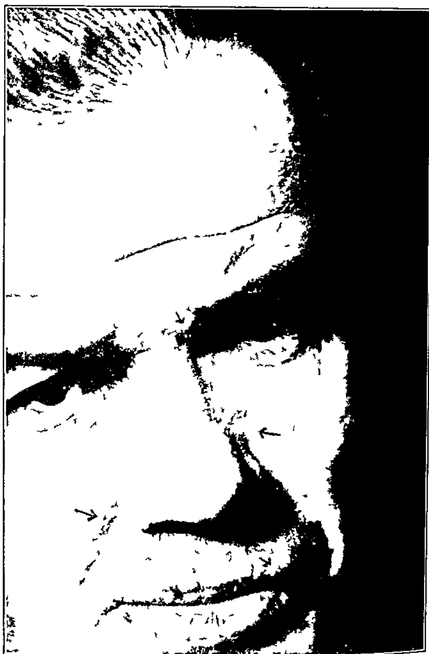


FIG 12 — Horny concretions in the orifices of the sebaceous glands of the face as indicated by the arrows The ordinary pellagrous dermatitis is shown on the left forehead (Courtesy of Dr David T Smith of Duke University)

laments Two weeks later a second and more severe set of symmetrical trophic ulcers appeared and got worse for 6 weeks when insulin was given to aid the patient s appetite the ulcers healed in two weeks

Lynch has reported 2 cases and Kelly and Rutledge 1 of epithelioma developing in pellagrous skin lesions but all the reports comment on the rarity of the association of the two conditions

Manifestation in the Alimentary Tract

Mouth — Stomatitis is one of the most frequent findings in pellagra Many patients complain bitterly of sore mouth while in others the subjective symptoms are slight Along with this the *tongue* usually is involved with similar subjective complaints Its physical appearance is often of great importance strongly suggesting a niacin deficiency It is usually beefy red without a coat but has been described as large and indented firm with bright red edges etc The fungiform papillae often are prominent and somewhat enlarged making what Lavinder and Babcock called a stipple tongue In other cases they may atrophy Very painful aphthous ulcers may develop along the margins at the tip and on the under surface of the tongue Fissuring often occurs A pellagrin who uses snuff which many do will often have a heavy coating of that material on the tongue In our High Point series 70 64 per cent of the patients complained of a sore mouth or tongue

The *salivary glands* may show general swelling and tenderness Sandwith found bilateral parotid enlargement in 4 per cent of his cases Suppuration does not occur Sullivan and Jones note the following points in regard to the saliva in pellagra 1 The specific gravity tends to be high 2 The total solids ash organic matter and mucin tend to be high but bear no relation to mouth symptoms 3 The diastatic power varies within normal limits 4 The sulfocyanate content is much less marked than in the saliva of normal persons 5 The reaction is somewhat more alkaline than normal Cheilosis may be due to niacin deficiency as mentioned in the section on Chemistry Secondary infection of the mouth with Vincent s organisms or with monilia is frequent

Esophagus — Pain on swallowing is not infrequent Burning in the esophagus may be a complaint Fisher made esophagoscopic examinations on 17 pellagrins All showed intense hyperemia of the mucosa and some showed edema Nine showed multiple tiny ulcerations Barium studies of the esophagus in 8 cases showed many small constricted areas along the course of the esophagus occurring in areas where ulcerations were found by the esophagoscope Fisher notes that the dysphagia resulting from esophagitis may cause serious deficiency in general nutrition and the experience of the present authors confirms this The esophagitis in all of Fisher s cases cleared up promptly on 150 mgm of niacinamide 15 mgm of thiamin chloride and 15 mgm of riboflavin daily for 3 months

Stomach — Gastric symptoms are common Anorexia may be very troublesome Nausea and vomiting may be obstinate although serious vomiting is infrequent Often gastric pain and distress are prominent In severe cases feeding may be difficult and treatment may have to be given parenterally In our High Point series 8 76 per cent of the patients complained of vomiting whereas only 5 51 per cent complained of nausea i e some had vomiting without nausea. Anorexia was noted by 3 67 per cent, sour stomach" by 2 75 per cent and a "weak feeling in stomach' by 1 patient

Practically all authorities note the frequency of achlorhydria or hypochlorhydria Turner found achlorhydria in 82 5 per cent of a group of cases Guthrie states that Angostini in 1893 noted both hypochlorhydria and hypopepsia with catarrh of the mucosa of the stomach and weakness of its motor power While the total acidity is normal in some cases, it averages less than half the normal amount An excess of hydrochloric acid has been described, but this is unusual Histamine has little or no effect on pellagrous achlorhydria Mulholland and King believe that the achlorhydria of pellagra usually but not always, is permanent They are unable to see any correlation between the achlorhydria and the clinical symptoms Biggam and Ghalioungui find no relation between the degree of involvement of the nervous system and the condition of the gastric juice

Spies and Payne have shown that the achylic' (achlorhydric?) gastric juice from 2 cases of acute pellagra that received a diet free of niacin produced an anti anemic substance, when incubated with beef as shown by a characteristic hematopoietic response in 2 patients with pernicious anemia Salah demonstrated the hemopoietic principle in the gastric juice of 5 pellagrins after injecting histamin Helmer Fouts and Zerfas found pepsin and rennin in the gastric mucosa of persons dying of pellagra although in smaller quantities than in controls dying of cardiac failure or pulmonary embolism This was true in one case that showed an absence of both during life even after histamine stimulation

Intestines — Formerly diarrhea was a hallmark of pellagra but the clinical picture of pellagra has changed greatly within the professional lifetime of the senior author The epidemic outbreak of pellagra as an acute often fulminant and rapidly fatal disease has been mentioned in the section on History At that time the "3 Ds" diagnostic triad was often mentioned meaning dermatitis diarrhea and dementia Some even added a 4th D, viz death Today the triad is unusual and the tetrad rare An early series of Wood s showed diarrhea in 77 per cent In a later series of 200 cases published in 1927, Wood noted 113 with diarrhea 56 5 per cent In our High Point series only 26 51 per cent showed diarrhea contrasted with 36 7 per cent showing constipation Many had normal bowel activity Extreme diarrhea such as used to occur in fulminant cases did not occur in our series Such cases as have extreme diarrhea usually are severe in all their manifestations They show very frequent liquid stools at any and

all times of day Pain and tenesmus may be severe Hemorrhage from the bowel has been reported several times and Wood saw one fatal hemorrhage Formerly it was not unusual for patients to state that they had had diarrhea in the spring for 2 or 3 years before the appearance of skin lesions led to the diagnosis of pellagra

Gas usually without obvious distention may be an early and obstinate complaint Burning sensations occur throughout the alimentary tract from the mouth to the rectum in various cases 16 51 per cent of our High Point series complained of gas while 58 72 per cent noted burning or hurting in the abdomen These groups were not broken down into cases of gastric vs those of intestinal origin as often it was impossible to differentiate between them

Careful study of the feces is important in pellagrins with intractable diarrhea Wood noted that in Egypt intestinal parasites were found very often in pellagrins and this is true of course in all localities having a heavy parasitic infestation of the general population Obviously it is important to discover and cure a complicating amebiasis Such a diagnosis can be made only by a well trained observer as there are many possible sources of error It is probable that amebiasis in pellagra has been reported when it was not present Antiamebic treatment of course will not cure pellagra but is essential in curing the patient who has both diseases Hookworm infection may complicate the picture

It is interesting to note that the feces in pellagra show normal utilization of fat and nitrogen This is proved by the use of the Schmidt Strassburger test diet This finding is important in differentiating sprue with which pellagra often has been confounded The senior author had a very interesting case in a 69 year old woman For four years prior to any eruption whatever she presented a typical picture of a case of irritable colon or so-called mucous colitis without diarrhea but with obstinate constipation and episodes of painful passage of large amounts of mucus from the bowel Along with this there was some stomatitis The diagnosis was not made until the eruption appeared when both the eruption and mucous colitis yielded to yeast and dietary treatment Sydenstricker says that ulcerative colitis may complicate pellagra

Pancreas —The pancreatic tissue of the patients just mentioned contained normal amounts of tryptic amylolytic and lipolytic enzymes as compared with controls

Liver —Slatineanu and his associates found hepatic insufficiency in 55 out of 62 cases J H Smith notes that the urea ratio is low enough to suggest such insufficiency He also notes that intestinal putrifaction is increased

Nervous Manifestations

These may appear at any time during the course of the disease Neurological physical signs rarely appear at the very onset of the disease although they have been reported as preceding all others

Subjective symptoms appear early Often the patient complains bitterly of vertigo a classical sign since the earliest accounts which is still seen frequently in the mild pellagra of today It was the commonest nervous symptom in our High Point series, 71 56 per cent of the patients showing it Paresthesias, hyperesthesias, muscle weakness tenderness in various parts, especially along the spine headache and pain in the back of the neck may be complaints Wood noted severe pains in the hands and feet which opiates failed to relieve The present authors have not encountered this symptom in such extreme degree Uncertainty of motion and a tendency to stagger are common and may persist well into convalescence Gregor quoting Tonnini's work, mentions mechanical muscular irritability suggestive of tetany spastic gait, diminution of thermal, tactile and faradocutaneous sensibility, etc

The tendon reflexes vary greatly Usually in the modern mild form of pellagra they are normal The most frequent abnormality is an increase but they may be decreased or rarely absent, especially the patellar reflexes They may vary on the two sides, one knee jerk being absent while the other is normal, one exaggerated with the other normal or decreased etc Other tendon reflexes may vary similarly in the same person at the same time A positive Babinski sign has been described S R Roberts having reported a unilateral case

Coarse tremors of the extremities head and tongue are noted P V Anderson noted athetoid movements also clonic convulsive movements giving way to tonic spasms which would last for a few seconds followed by a period of quiescence before the clonic movements began again Muscular cramps were noted in half of B R Tucker s cases and occurred in the abdomen legs, arms thighs and back Gregor stresses the muscular spasms, and his experience agreed with that of Tonnini who found tonic spasms in the terminal stages of the disease Gregor gives the following account of one of his cases "The patient lies stiff on his back elbow and wrist joints flexed also the knees, the feet show plantar flexion In all extremities severe spasms are present Complete extension is impossible The upper arms are abducted and adducted in jerks the hands perform slowly extreme rotations When drinking motions are made by the patient he tries in jerks to bring his hands to his mouth visibly combatting the involuntary contractions of his arms and hands At last he succeeds in bringing the wrist joint of the spasmodically flexed right hand near the mouth The same spasmodic phenomena continued the next day The head too is held in maximum spasmodic lateral rotation On the next day on which death occurred I observed jerkings of large muscle bundles of the lower half of the face and of the forearm "

Gregor reports the following case to illustrate the occurrence of clonic spasm 'In the morning the patient lies on her back, the eyes closed the upper arms adducted the forearms flexed at an angle of 90 degrees which positions are kept fixed In the region of the left lower facial nerve I observed fine tremors, which

do not lead to any motor effects also others coarser ones which draw the whole half of the mouth downward The same tremors also are observed although less severely in the right lower facial nerve The mouth is drawn a little to the left Similar tremors of fine and coarse muscle fibers also are noticed in the sternocleido mastoid and pectoralis on both sides The upper arms perform abductions and adductions in a jerk like manner and the lower arms flexions and extensions The thumbs now and then are adducted in spasms the fingers flexed again characteristic of tetany Similar spasmodic movements are observed also in the lower extremities Passive movements find spastic resistance everywhere The pupils react promptly to light and are of equal size reflexes are increased involuntary defecation and micturition occur The patient does not respond when called by name the face is distorted when pain is inflicted the condition slowly disappears until the next day Such descriptions must seem almost fantastic to young physicians unfamiliar with the fulminant pellagra of a generation ago but the senior author saw many such cases in his early practice

Definite ankle clonus may be noted It is less frequent in the mild types of today than in the severe epidemic cases Light percussion on a tendon has been known to start a spasmodic reaction of the part accompanied by convulsive movements of the whole body suggesting strychnine poisoning A breath of air or sunlight has been said to provoke motor disturbances including tonic spasms Skin reflexes may vary in different cases and on the two sides in the same case The pupils may react normally to light or be sluggish One case was reported with a lack of reaction to light but the report did not exclude other causes of this phenomenon

Anesthesia of the skin was noted a number of times Tardy replies to tests for various types of sensation are common but usually are due to mental retardation B R Tucker noted muscular wasting in over half of his patients Strangely enough Wood reported that it did not occur in his patients In the severe cases seen by the senior author generalized muscular wasting was the rule toward the end but probably was due to starvation from inability to utilize food This is rare today with the mild form of pellagra and modern therapy

Epileptiform seizures are infrequent Wood saw them in one case but necropsy showed capillaries of the brain filled with malarial pigment The patient had been treated for malaria but had suffered a relapse Neusser reported a case of amyotrophic lateral sclerosis in a pellagrin but whether it was a pellagrous phenomenon or a purely coincidental disease is not clear One of Wood s fatal cases presented a classical picture of Landry s paralysis Multiple neuritis occurs but is due to an associated thiamin deficiency Clinically as well as pathologically the cord changes may produce a typical picture of subacute combined degeneration

Wood reported a case in which the vibration sense was decreased over many

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in 41 28 per cent of our cases in the lower extremities in 7 52 per cent all over the body in 9 17 per cent in the abdomen in 2 75 per cent and in one case each in the back left side from the waist down respectively These took the form of numbness and tingling In addition to these there were complaints of roaring in the head rushing of blood to the head not due to niacin and queer feelings in the eyes each in one case One patient made the very interesting statement that the muscles in her arms felt as if there were little bells ringing in them Weakness was complained of in 76 15 per cent of our cases

Mental Disturbances

Many cases of pellagra exist for years without mental symptoms especially in children However the mental changes in pellagra are of great importance Symptoms of depression often follow closely on the restlessness vertigo and insomnia Gregor divided the mental manifestations into seven types as follows

1 *The mild neurasthenic type* The salient features of this type were depression unrest a fear of impending trouble and hypochondriacal ideas This is by far the commonest type seen today the more severe types having largely disappeared

2 *The severe neurasthenic type* The patient lies apathetically in bed appearing well oriented at first but later becoming disoriented There is marked mental retardation Answers to questions may be given so slowly that by the time they come the questioner has forgotten what he asked

3 *The moderately delirious type* This presents a picture varying from distressing hallucinations vivid emotion and violent motor excitement to somnolent states with muttering delirium Often this progresses into the 5th type mentioned below

4 *The intensely delirious type* The patient shows an acute delirium quickly followed by death

5 *The katatonic type* This is characterized by excitation with stereotyped actions wild jactitation and verbigeration with rapid transition into dementia in which posture and motion sterotypies impulsive actions incoherent talk negativism flexibilitas cerea etc make up the picture

6 *The anxiety psychosis type* This type Gregor called *anxiety psychosis* though *melancholia* would seem a better term There is a marked sense of insufficiency with ideas of persecution and the sense of some great sin with hallucinations in some cases appearing in episodes with a slight stupor between them Wood found a large proportion of his cases to be of this type

7 *The manic depressive type* Gregor had 2 cases of this type One showed mania the other melancholia changing into mania although later the patient became stuporous

bony points, including the lower parts of radius and ulna anterior superior spine of the ilium crest of the tibia internal and external malleoli and sternum There was no decrease over the sacrum, however, and Wood considered this a differential point from tabes in which he found greater decrease of the vibration sense over the sacrum than anywhere else Bowel and bladder sphincter control may be lost as may the abdominal reflexes

Fine and Lachman reported 3 cases of alcoholic pellagra showing retrobulbar neuritis and wondered if this were not merely due to a thiamin deficiency plus alcohol Blankenhorn reported a case of alcoholic pellagra with clonic twitching of the extremities, chiefly the lower plus opisthotonos incontinence of urine and striking mental excitement but without unconsciousness The patient recovered on high caloric diet, intramuscular liver extract and yeast

Dorogan and Capri noted a difficulty with voluntary movements even of the tongue characterized by a remarkable slowness, which they believed due to a hypertonicity of the muscles On this supposition they studied the muscles in functional groups from the viewpoint of chronaxia according to the method of Bourguignon Their conclusions are as follows (1) the chronaxia of the muscles of the upper extremity is diminished sharply in pellagra, (2) in the lower extremities in general there is an increase in the chronaxia of the muscles of two groups and a decrease in that of the muscles of a third group, (3) there is a tendency to equalization of the chronaxia of the muscles of anterior and posterior groups in the same segment of either upper or lower extremity, (4) the myograms of all muscles examined showed a tonic form of contraction of great duration apparently double or triple the normal duration The investigators reason from this that in pellagra a certain degree of more or less generalized hypertonicity becomes established in the muscular system Along with this goes a decrease to below the normal time of the chronaxia of the corresponding muscles The authors quote Lapicque and Bourguignon to the effect that this combination of factors is analogous to similar factors found to co-exist in parkinsonism

Sydenstricker noted that increased sensitivity to pain is common in pellagra. Pressure on the calves may be painful, and stroking the skin with a needle may cause a stinging sensation for many minutes Niacin cures these symptoms but will not prevent their recurrence unless continued indefinitely

In our High Point series in addition to vertigo mentioned above we noted exaggerated knee jerks in 9 17 per cent of the cases sluggish in 2 75 per cent and the following signs in one patient each, absent knee jerks, intention tremor, ataxic gait tremor of hands and feet Pains in the head occurred in 13 76 per cent, in the feet and legs in a like number in the back in 4 59 per cent in the chest in 3 67 per cent and in one patient each we had complaints of pain in the eyes, back of neck throat fingers and feet left flank all over the body, respectively Paresthesias were very frequent, occurring in the upper extremities

partial deafness especially for high pitched tones a non specific vaginitis with hyperesthesia and dyspareunia photophobia burning and itching of the eyes dim vision and a superficial vascularizing keratitis seen best with the slit lamp The eye signs he considers due to an associated riboflavin deficiency He has noted mydriasis with consequent photophobia in a pellagrin that cleared up on riboflavin

Osseous System

A number of authors mention abnormally brittle bones pains in the joints and long bones arthritis of varying types etc Whether these phenomena are integral parts of the pellagra picture or merely coincidental is uncertain The present authors lean toward the latter view

Urine

Routine analysis shows nothing characteristic of pellagra Other urinary findings will be discussed under the heading of Metabolism

Blood

Turner found the total blood volume below ideal values in 82 per cent of the cases studied by him and above ideal values in 17 5 per cent Low values may be attributed to diarrheal dehydration Turner studied the erythrocytes in 50 pellagrins In 56 per cent he found no appreciable anemia in 16 per cent slight or questionable in 12 per cent moderate and in 4 per cent very severe Among those with severe anemia other diseases which might affect the blood were common Diarrheal patients did not seem more anemic than non diarrheal but hemoconcentration might mask this The anemia was definitely of the chlorotic normocytic or microcytic type and in no instance macrocytic 34 per cent of the patients had a low corpuscular hemoglobin concentration while in 66 per cent it was within normal range The average size of the red cells tended to diminish in proportion to the severity of the anemia Many authors however report a macrocytic anemia especially in alcoholic cases perhaps due to associated liver damage Its incidence varies in different parts of the world In Egypt Salah found none Huck and Turner found it uncommon in endemic areas of the United States whereas Spies and Shen found it relatively common in alcoholic pellagrins No characteristic changes have been noted in the leukocytes Other blood changes will be considered under the next heading

Dr Erle Craven of Lexington N C reported a severe case of pellagra with extreme hypochromic anemia and multiple thrombi in the superficial veins of the legs He was uncertain whether the thrombi represented a true complication or whether they were coincidental (personal communication)

Many cases fail to fit into this classification Often the only mental sign is apprehension Depressed states with memory defects are frequent Many of Wood s cases refused food, although in one of these patients if a glass of milk were left beside her bed as soon as she thought she was unobserved, she would drink it all with the expression of a child stealing cake Wood reported 1 patient with an abnormal craving for food of any sort

In his original chapter on pellagra in this work published shortly after the close of World War I Wood stated that in North Carolina it was estimated that 40 per cent of pellagrins became mentally disturbed to a degree requiring institutional treatment Certainly this is far from true at the present time It is further evidence of the striking change in the picture of pellagra in the past quarter century that not a single one of our High Point Clinic series had to be committed to a psychiatric hospital On the other hand in the early days of practice of the senior author psychiatric commitment of pellagrins was not infrequent, provided the patients lived long enough In our clinic series mild mental symptoms were the rule severe ones exceptional We tabulated them as follows

	% of all cases
General nervousness irritability fearfulness worry	43 1
Forgetfulness or confusion	33 94
Insomnia	33 03
Definite history of a psychosis in the past	7 34
Fear of going crazy	5 50
Depression (moderately severe), blind spells delirium, somnolence general shaking (1 case each), each	0 91

Mental symptoms may appear at any time during the disease They may be first symptoms noted, many appear at the height of the disease may not appear until convalescence or may be absent throughout In the old epidemic days the picture of a rapidly developing profound stupor with death in a few days was not unusual but we have not observed such a case within the past 2 decades

Cronin reported a remarkable case of alcoholic pellagra with retinal hemorrhages in addition to a bizarre psychosis showing an extraordinary variety of crude sexual hallucinations in which he would see women and children come into the hospital in pairs and get into beds and practice all manner of perverse sexual acts and also would see the hospital beds cantering like horses and spurting spermatic fluid from the mattresses Then a nude mother would appear and try to strip her 6 year old daughter and offer her as a prostitute etc These hallucinations disappeared as the pellagra cleared up The present authors would tend to regard this as an acute alcoholic hallucinosis complicated with pellagra, the two conditions clearing up simultaneously, rather than as an integral part of the pellagra

In addition to symptoms mentioned Sydenstricker has noted confabulation,

to activate fully the trypsinogen of the pancreatic tissue Tsatsakos studied the pyruvic acid content of human blood in pellagra He found normal persons to have a value of under 0 4 mgm per 100 c c of blood and pellagrins a value of 1 0 to 1 6 mgm per 100 c c He concluded the increase was due to incomplete decomposition of pyruvic acid in the body

Roentgenological Findings

Ruffin Baylin and Cayer found definite alterations of the small intestine x ray pattern to be common in frank deficiencies of the B complex and in sprue but found similar alterations in apparently normal people with neither clinical nor laboratory evidence of any deficiency state so feel that minor changes in the pattern of the small intestine should be interpreted with caution

Seasonal Variations and Duration of the Disease

The seasonal variations of pellagra are extremely important With the first appearance of frost the disease tends to become latent and the remission lasts until spring Then the symptoms are likely to recur and increase as the weather gets warmer unless controlled by therapy and again clear up in the fall with the reappearance of frost Our High Point Pellagra Clinic sponsored by the local chapter of the American Red Cross operated for two seasons from April 16 to October 15 only in the years 1939–40 and 1940–41 Our detailed statistical analyses were made for the first season The clinic closed permanently in 1941 because the pellagra problem was being solved rapidly and patients constantly were getting fewer and the disease milder There was no reason to operate the clinic during the winter months as the patients were in remission and had no need of treatment We believe that the clinic served a valuable purpose but control observations in communities without such clinics also show a very striking decrease in the disease suggesting the operation of other factors

The duration of the disease has been extremely variable in the past being anywhere from a few weeks or less in fulminant fatal cases to many years In the High Point Clinic series we found the following from the histories of the patients

Duration of Disease	*% of Cases*
Less than 1 year	2 75
1 year	11 93
2 to 5 years	33 03
6 to 10 years	29 36
11 to 20 years	18 35
21 to 30 years	4 59
Indefinite	1.83

The longest duration was 30 years (1 case)

Metabolism

A study of the reports of many investigators reveals the following points of interest The total urinary nitrogen and the urinary excretion of uric acid and phosphorus pentoxide tend to be low Smith found the alkali reserve of the blood normal Disturbances of the acid base equilibrium are uncommon There is a tendency toward low serum albumin concentration, which may remain long after the outward manifestations of the disease have disappeared, this probably is due to the prolonged inadequate intake of protein as well as liver damage and disturbed hepatic function There may be an excess of polypeptids in the blood which is attributed also to hepatic insufficiency The creatine coefficient i e ratio of excretion to body weight is much below normal and remains low during convalescence It is low in proportion to the clinical severity of the disease Small amounts of creatine are eliminated in the urine Purine metabolism is normal

Spies and his co-workers studied the cerebral carbohydrate metabolism in pellagrins by measuring differences of oxygen glucose and lactic acid between the femoral artery and internal jugular vein and felt that the A V oxygen difference was somewhat lower than normal Where pellagra is associated with beri beri a more marked depression of A V difference was noted They felt there was a diminution in cerebral metabolism, which might afford a basis for the mental changes

J H Smith gives the results of the work of Kock and Voegtlin in a chemical analysis of the central nervous systems of five uncomplicated cases of pellagra These showed increased water decreased lipoids, slightly decreased proteins and decreased cerebrosides phosphotides and sulphatides probably due to an increased lipolytic process There was a relative increase in the cholesterol in the cerebrum There was a considerable increase in nitrogenous non colloidal extractives

G R Morey studied the antibody response of patients with pellagra to antigenic stimulation with *B tularense* and found it to be less than in normal persons He also states that those with the most marked deficiencies had least ability to retain titers Payne and Perlzweig using normal controls found that in 14 cases of pellagra with extensive dermatitis there was a marked reduction in the cystine content of the finger nails without appreciable change in their total protein content With subsidence of the dermatitis the cystine content of the finger nails returned to normal In severe pellagra without dermatitis and in partially cured cases there were no marked changes in the cystine content of the finger nails. Helmer Fouts and Zerfas found the pancreatic tissue of pellagrins to contain normal amounts of tryptic amylolytic and lipolytic enzymes as compared with controls The duodenal mucosa of the pellagrins produced sufficient enterokinase

apt to be affected Pruritis is marked papules are frequent *Contact dermatitis* usually is vesicular and a history of exposure to some irritant usually is elicited The diagnosis is substantiated by a positive patch test to the suspected substance In addition the lesions of *contact dermatitis* and *allergic dermatitis* usually are less sharply demarcated than those of pellagra and resolve more rapidly and without pigmentation *Erythema multiforme bullosum* may present some difficulty in differential diagnosis but usually is accompanied by fever The lesions are more extensive on the extremities not confined to the exposed surfaces and are found frequently on the body particularly the back The bullous lesions of pellagra are always on an erythematous base while those of *erythema multiforme* may appear surrounded by normal skin Older persons who have lived an outdoor life may have senile atrophy of the skin of the dorsum of the hands with thinning and pigmentation This if accompanied by a non specific colitis may resemble pellagra In general however the distribution and symmetry of the lesions and the relation to sunlight heat and trauma as well as the presence of gastrointestinal and central nervous system manifestations aid in the diagnosis

The closely allied nutritional disorders of sprue and pernicious anemia may at times cause some confusion The symptoms of stomatitis glossitis papillary atrophy macrocytic anemia and gastrointestinal disturbances may be common to all three and there is some evidence that a deficiency of the B complex may occur in all It should be remembered also that cases of coexisting pellagra and pernicious anemia and pellagra and sprue in the same patient have been reported Sprue manifests no skin lesions the tongue usually is different excessive salivation does not occur and the disease is accompanied by marked wasting In pellagra utilization of fat and nitrogen as demonstrated by investigation of the stool is normal Sprue can be recognized by the steatorrhea and flat glucose tolerance curve In sprue tetany is a frequent accompaniment due to lowering of the ionized blood calcium as is the marked lowering of fat soluble vitamin A and carotene in the blood plasma

Although the incidence of achlorhydria may be frequent in pellagrins as well as the finding of macrocytic anemia it can be shown that the pellagrin does not lack the intrinsic antianemic factor In addition the serum bilirubin is within normal limits and the serum iron usually is not elevated These findings as well as the absence of skin lesions serve to differentiate pernicious anemia

The steadily decreasing incidence of full blown pellagra has turned attention to the milder deficiencies which now are seen most frequently Much has been written concerning so-called subclinical pellagra In many instances the diagnosis is made solely on the basis of an inadequate diet and such indefinite symptoms as weakness vague digestive complaints particularly esophageal and epigastric burning anorexia and emotional disturbances Evans reports the case of a patient with a prolonged psychoneurosis who finally developed a frank psychosis

We also analyzed statistically the number of recurrences from the case histories

No of Recurrences	% of Cases
1	18 35
2 to 5	25 69
6 to 10	20 18
11 to 20	9 17
Over 20	3 67
None	22 94

The figures in the last two tables may seem somewhat discrepant, but the explanation is that some pellagrins reporting no recurrences did so because, although there was a marked remission during the winter months they did not feel completely well and believed that they continued to have the manifestations of the disease throughout the year

Diagnosis

The diagnosis of pellagra is not difficult when the case is typical The history of an inadequate diet particularly in protein, usually is obtained The patients usually present the symptoms of loss of appetite sore mouth and tongue, paresthesiae and erythema or frank dermatitis The diagnosis should be suspected even in the absence of dermatitis, when depression, emotional and oral changes are present Changes in the mouth and tongue are early findings There is an increase in color as well as papillary atrophy of the tongue usually beginning at the margins The fungiform papillae may become unusually prominent and as the disorder progresses the tongue may become entirely denuded, and superficial ulcers appear These changes are paralleled by those of the mucous membranes, and cheilosis may appear also The development of the characteristic skin lesions is felt by many to be necessary for positive diagnosis In many instances probably this is well justified The presence of the typical symmetrical lesions over the face, neck wrists hands, feet and often, the genital regions usually presents no difficulty in diagnosis

Pellagra may be confused at times with other skin conditions The erythema of mild or early cases may be confused with sunburn particularly if it is associated with a non specific diarrhea The pellagrous erythema may be distinguished from practically all other dermatoses which otherwise resemble it, by its seasonal incidence appearing as it does in the spring and early summer and disappearing as a rule by the time of the first frost Advanced cases that will not disappear in winter should give no difficulty in diagnosis Kirby gives the following differential points distinguishing pellagra from certain other skin conditions In *erythematous eczema* the face, axillae groins and flexor surfaces of the forearms are

become so in the United States The pre-existence of tuberculosis amebic or bacillary dysentery hookworm disease etc may influence the course of the disease greatly The frequency of these conditions especially of hookworm disease in the southern United States at the time of the epidemic outbreak of pellagra and their greatly lessened incidence at the present time may well be the chief explanation of the change in the character of pellagra The first effective treatment adequate diet improved the prognosis for those who were able and willing to change their dietary habits and who did not have too serious a form of the disease Some could not take food because of vomiting others could not utilize it because of severe diarrhea Very many pellagrins being both poor and ignorant found it too difficult to change the habits of a lifetime and gave up the struggle The advent of yeast treatment helped some although the original bitter yeast was so distasteful that many literally could not stomach it and preferred death to the treatment Debittered yeast was another advance but was somewhat more expensive and most pellagrins were very poor When niacin became available however it was at once the most effective and least expensive method of treatment as well as easy to take and it played a very important part in improving the prognosis of pellagra

Years ago Wood stated that from 17 to 20 per cent of pregnant pellagrins aborted The increased metabolic demands of pregnancy usually make a co-existing pellagra worse Menorrhagia and metrorrhagia are frequent in pellagra and play their part in weakening the patient Surgical operations may precipitate an acute exacerbation of a latent case perhaps due as much to conditions associated with operations such as lessened food intake anesthesia intravenous glucose etc as to the operations themselves Only emergency surgery should be performed in uncontrolled pellagra

With severe nervous and mental manifestations especially with extensive involvement of the spinal cord the prognosis is grave This is also true to a somewhat lesser degree with intractable vomiting and diarrhea although with parenteral methods of niacin treatment it is less so than before such treatment was available A patient who will not adopt proper dietary habits is extremely likely to relapse when active treatment is stopped Sudden death may occur in acute pellagra In general today the disease is mild and prognosis good

PROPHYLAXIS

The most essential thing in the prophylaxis of pellagra is an adequate diet Many years ago Lombroso said that if a pellagrin could and would choose a proper diet the disease would not occur It was recognized that in most instances pellagra and poverty went together As the poor peasant or sharecropper never had a really ample diet it was important that he be given a practical diet that he

without skin lesions but with a slightly red tongue and oral mucosa, which cleared up in a few days on niacin Frostig and Spies note that, while it has been known for many years that pellagrins in relapse manifest psychotic changes there is less frequent recognition of the association of so-called psychoneurotic symptoms with subclinical and mild pellagra They feel that these symptoms have certain distinctive characteristics which are helpful in early diagnosis, since they follow a common pattern They classify these symptoms into an elementary syndrome of psychosensory, psychomotor and emotional disturbances and general central nervous system symptoms such as weakness increased fatiguability, sleeplessness and headache Meyersburg notes that a senile psychosis may be simulated by a pellagrous encephalopathy in the aged, and that vitamin B complex helps such patients

It is obvious that early diagnosis before the appearance of the fully developed, unmistakable syndrome of pellagra is of the greatest importance In the diagnosis of mild forms of nutritional disease clinical manifestations must be supplemented by other procedures The development in recent years of laboratory procedures for the measurement of vitamin levels in blood and urine may afford a better understanding as well as a more accurate diagnosis and sharp delineation between patients having early manifestations of the disease and those in whom symptoms and findings are unrelated to a deficiency state and in whom vitamin therapy is futile and unjustified The interpretation of these biochemical tests still requires more adequate correlation in human subjects

The relationship between the clinical picture of a mild or early vitamin deficiency and laboratory determinations of vitamin levels was undertaken by Ruffin Cayer and Perlzweig and is discussed in the section on Chemistry This work showed a definite relationship between the clinical picture of an early B complex deficiency and the vitamin levels as determined in the laboratory While such procedures still are not within the scope of the average laboratory and certain variants undoubtedly remain and must be worked out such work does point out the way in which more early recognition is possible, since the chemical and biological alterations may precede clinical and physical changes by a considerable time interval

Prognosis

The prognosis of pellagra has changed greatly since the first appearance of the Oxford Medicine in 1919 When the disease broke out in epidemic form in the southern United States, its violence was unlike anything in the literature and indeed greatly delayed its recognition as pellagra Death in from 4 to 8 weeks was not unusual, recalling the fulminance of the outbreak of measles in the Fiji Islands when the British ship *Dido* called with the disease aboard In modern times pellagra has been a chronic disease in Italy, and in recent years it has

become so in the United States The pre existence of tuberculosis amebic or bacillary dysentery hookworm disease etc may influence the course of the disease greatly The frequency of these conditions especially of hookworm disease in the southern United States at the time of the epidemic outbreak of pellagra and their greatly lessened incidence at the present time may well be the chief explanation of the change in the character of pellagra The first effective treatment adequate diet, *improved the prognosis for those who were able and* willing to change their dietary habits and who did not have too serious a form of the disease Some could not take food because of vomiting others could not utilize it because of severe diarrhea Very many pellagrins being both poor and ignorant found it too difficult to change the habits of a lifetime and gave up the struggle The advent of yeast treatment helped some although the original bitter yeast was so distasteful that many literally could not stomach it and preferred death to the treatment Debittered yeast was another advance but was somewhat more expensive and most pellagrins were very poor When niacin became available however it was at once the most effective and least expensive method of treatment as well as easy to take and it played a very important part in improving the prognosis of pellagra

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Dann has calculated that the minimum daily niacin requirement of a 70 kg man is probably less than 10 mgm but that the amount must be somewhat increased for those in whom the chief cereal of the diet is corn This is definitely lower than the minimum daily allowance recommended by the National Research Council of 18 mgm However, Dann feels that there is so far insufficient evidence to justify an alteration at present from the latter figures which allow a factor of safety

One of us (D C) has prepared a table showing the niacin values of certain common foods The amounts of the foods given represent in general ordinary serving portions

NIACIN VALUES OF FOODS

Food	*Amount*	*Value in mgm*
Liver (pork)	4 oz	24
(beef)	4 oz	16 to 23
(veal)	4 oz	13 to o
Pork	4 oz	10 6
Fresh ham	4 oz	7 to 8
Smoked ham	4 oz	4 to 8
Poultry	4 oz	7 7
Beef	4 oz	7 to 8
Beef kidney	4 oz	6 to 8
Beef heart	4 oz	7 to 8
Bran	1 oz	8 8
Peanuts	1 oz	5 3
Whole wheat bread	4 oz	3 3
Whole wheat cereal	1 oz	1 8
Enriched bread	4 oz	1 7
Corn bread	5 oz	0 9
Rye (whole)	4 oz	13 to 14
Rye flour (dark)	4 oz	12 to 13
Soybean flour	4 oz	2 4
Corn meal	4 oz	0 6 to 0 7
Rolled oats	4 oz	1 4 to 1 6
Barley flour	4 oz	5 5 to 6 5
Salmon	4 oz	8 4
Canned shrimp	4 oz	0 8
Canned oyster	4 oz	0 7
Canned clam	4 oz	1 1
Tuna	4 oz	10 2

could afford and that would combat the deficiency A person may be underfed and escape pellagra or eat large amounts of the wrong kind of food and develop it If the remedies are expensive meats, it is obvious that just as in Lombroso s day the patient need not hope for relief, but if inexpensive food will protect him, much will be accomplished

I resh lean meat notably beef also mammalian liver and canned salmon are the most valuable pellagra preventing foods However, economic conditions often exclude much beef or liver The value of milk and eggs has been greatly over estimated in the past They should not be allowed to supplant an adequate supply of meat The junior author has seen a patient with active pellagra who was drinking 4 quarts of milk daily, who responded promptly to adequate doses of niacin Legumes green vegetables, etc are useful but should not be relied upon to the exclusion of the more important meat Inexpensive cuts are effective In 1934 Sebrell published a table showing the anti pellagra value of many foods Briefly summarized it showed

MEATS AND FISH

Good Fresh beef canned corned beef canned chicken, dried pork liver lean pork shoulder rabbit canned salmon

Fair Canned haddock

None Salt pork

DAIRY PRODUCTS

Good Buttermilk

Fair Fresh skim milk dried skim milk evaporated milk

Slight Butter leached casein

CEREALS

Slight Whole wheat

None Whole white corn meal rolled oats rye meal

OILS AND FATS

None Cod liver oil cottonseed oil lard

VEGETABLES

Good Canned collards canned kale canned green peas juice from canned tomatoes canned turnip greens

Fair Red kidney beans soybeans canned green cabbage cowpeas canned mustard greens dried green peas canned spinach

Slight Canned green stringless beans carrots canned Cos lettuce canned green onions rutabaga turnips

None Evaporated apples dried prunes

MISCELLANEOUS

Good Liver (Minot s extract 343) peanut meal wheat germ (ether extracted) dried baker s yeast autoclaved baker s yeast dried brewer s yeast yeast vitamin powder

Fair Dried egg yolk

None Corn starch gelatin

recent years makes the problem of prophylaxis much less acute than formerly We believe that those who still show a tendency to pellagrous relapses should take 100 mgm of niacin daily from about the middle of April to the middle of October especially in the southeastern United States in addition to eating a diet containing at least 18 mgm daily A half ounce of debittered brewer's yeast may be used thrice daily taken in tomato juice or some other liquid to disguise the taste but it is far less pleasant to take than the niacin It may be needed in those with clinical evidences of multiple deficiencies of the B complex although tablets or capsules containing a potent B complex preparation are far pleasanter It should be noted that some commercial yeasts have been found to be lower in niacin content than others therefore a preparation should be used which contains at least 100 mgm in the daily dosage Liver preparations by and large are too expensive for the average pellagrin to keep taking over any considerable length of time Krehl Teply and Elvehjem finding that on a heavy corn grit diet the niacin requirements of man are probably at least 3 times as great as those on a synthetic diet or a whole milk ration suggested that milled corn products be enriched with considerably more niacin than had previously been thought necessary

Treatment

Niacin today is the sine qua non of treatment 100 mgm daily is an adequate dose for most patients If severe vasomotor flushing results the daily amount may be divided into two doses one taken after the morning meal the other after the evening meal The most economical method is to prescribe 100 mgm tablets and when divided doses are necessary have the patient take half a tablet at each dose All patients should be told at the beginning of treatment to expect that some sensation of general flushing and heat throughout the body may occur in 10 to 30 minutes after taking the niacin but that it is harmless *Niacinamide* in the same dosage is equally effective and is free from the unpleasant vasomotor reactions mentioned but is considerably more expensive and for that reason less applicable in treating pellagrins For those who can afford it it is the best treatment In addition many patients will require other components of the B complex notably thiamin and riboflavin It is doubtful if any of the other components are important but from a practical standpoint it usually is easier to give the whole B complex than to give the 3 essential components niacin thiamin and riboflavin separately The least expensive practical way to give this is by means of *brewers' yeast* giving from ½ to 1 ounce of debittered brewer's yeast thrice daily in some liquid as described under prophylaxis We have found tomato juice the most generally satisfactory liquid in disguising the taste Ordinary brewer's yeast which has not been debittered is even cheaper than debittered yeast but is of little practical value as its taste is so unpleasant that few

NIACIN VALUES OF FOODS
(Continued)

Apples	4 oz (fresh)	0.5 to 0.6
Bananas	4 oz (fresh)	0.6 to 0.7
Oranges	4 oz	0.23
Spinach	4 oz	0.7 to 0.8
Tomatoes	4 oz	0.5 to 0.6
Dates	4 oz	2.2
Onions	4 oz	0.1
Peaches	4 oz	0.95
Pears	4 oz	0.14
Potato (white)	4 oz	1.18
Yam	4 oz	0.8
Carrot	3½ oz	1.5
Dried beans, peas	1½ oz	1.3
Red beets	4 oz	0.64
Grapefruit juice	100 cc	0.21
Lemon juice	100 cc	0.08
Orange juice	100 cc	0.22
Tomato juice	100 cc	0.10
Skim milk	1 pint	0.89
Whole milk	1 pint	0.3
1 egg	1¾ oz	0.03

Variations are found in different samples of the same food. During the cooking of vegetables and fruits the loss of niacin ranged from 8 to 22 per cent. In addition, the cooking water ("pot liquor") averaged 12 per cent of the total niacin. The liquids associated with canned vegetables contained 30 to 40 per cent of the total niacin. Dann and Handler showed that only ½ to ⅔ of niacin present in raw meat generally will survive cooking and so be ingested. Most fruits and vegetables are not very good sources of niacin. On a dry weight basis carrots and tomatoes are best. Milk and eggs are poor sources, although skim milk is better than whole milk and buttermilk better than either. Lean meats in general, peanuts, beans and wheat germ are excellent sources. In the above table any food with a niacin value of over 4 mgm may be considered good, from 2 to 4 fair, under 2 poor.

Niacin itself has proved such an astonishingly effective and inexpensive therapeutic agent that it seems that it should be valuable in prophylaxis. Smith, Ruffin and Smith suggested that it could be mixed with table salt and sold in areas in which pellagra is endemic, similar to the distribution of iodized salt where goiter is prevalent. The remarkable reduction in the incidence of pellagra in

extreme cases opiates temporarily However it has been years since we have had a case requiring opiates Arsenic once thought of value is no longer advocated It may have cleared up complicating cases of Vincent s infection of the mouth but, despite the reports of J F Wilson and others seems of very little value in pellagra itself and reliance should be placed on the other agents mentioned above

Once successfully treated the patient must be instructed in future prophylaxis by urging that he remain on an adequate diet for life and take niacin prophylactically as recommended for several seasons at least

A number of substances related to niacin or thiamin have been used experimentally and successfully in treatment Bills McDonald and Spies showed that pyrazine 2 3-dicarboxylic acid and pyrazine monocarboxylic acid are antipellagric substances Vilter and Spies gave 6 pellagrins 1000 mgm each orally or quinolinic acid in divided doses over a period of 5 hours They responded dramatically although Woolley Strong Madden and Elvehjem reported that it did not cure canine blacktongue They did not however say which type of blacktongue was so treated Spies Vilter and Ashe found niacin niacinamide and sodium nicotinate all *effective They used 50 mgm doses from once a day up to a maximum* of 10 times a day using the large amounts in severe cases Sydenstricker Geeslin Templeton and Weaver reported cures of 2 patients with dermatitis cheilosis and conjunctivitis by riboflavin alone One of these received 50 mgm daily for 3 days the other 30 mgm daily (10 mgm t i d) for 4 days Lewy Himwich Frostig and Spies found that cocarboxylase thiamin pyrophosphate improved metabolism and affected the peripheral and cranial nerves in pellagrins with beriberi Lewy Spies and Aring treated 50 pellagrins showing neuropathy Of these 50 patients 75 per cent had polyneuropathy of the motor and sensory nerves 20 per cent *extrapyramidal signs half of these showing mild parkinsonism and 12 5 per* cent had tremor with pyramidal tract signs They found that the intravenous injection of 50 mgm or more of phosphorulated thiamin cocarboxylase in 9 of these patients caused improvement in 7 the patients becoming neurologically normal within 1 to 5 days but then regressing to their former condition The clinical effect of cocarboxylase was found identical with that of thiamin The 2 patients who failed to improve suggest that the neuropathic changes may be come irreversible No improvement was obtained in these neuropathies following the administration of riboflavin Vilter Bean and Spies found rapid improvement in pellagrins with peripheral neuritis who were given *adenylic acid* prepared from either yeast or muscle tissue but the reactions were so much more severe than those from niacin and thiamin that they do not advise its general use

Gilman and Gilman studying pellagra in infants in South Africa found extensive fatty changes in the liver and every one of 7 cases treated with vitamins including niacin died A liver extract rich in the Cohn fraction proved

will take it When the patient can afford it, one of the modern potent *vitamin B complex tablets or capsules* may be prescribed thrice daily, but the usual dosage of niacin should be given in addition, as the niacin content of the B complex preparations may not be adequate The patient should be instructed in the importance of an adequate supply of lean meat in the diet Cheap cuts are as effective as expensive ones Mammalian liver, when obtainable is especially valuable in the diet

Alport Ghalioungui and Hanna found niacinamide effective in Egypt in cases where diet or diet plus marmite a yeast like preparation known in this country as vegex had failed Smith and Ruffin calculated the therapeutic dose of niacin as 1 5 mgm per kilo of body weight parenterally, whereas 100 mgm thrice daily orally was advocated by them In recent years we have seen no pellagrins unable to take oral treatment, so confine ourselves to that In our High Point Clinic 100 mgm of niacin daily seemed adequate in most instances We gave this to 81 patients, yeast to 24 patients diet alone to 5 patients and hydrochloric acid to 1 patient In 6 patients or 5 5 per cent of the total, yeast was found clinically superior to niacin In the remainder, who were given niacin, it seemed superior to yeast We had 2 patients with peculiar reactions to treatment One complained that every time she took yeast her feet would break out in an eruption It was a papular eruption characteristic of neither pellagra epidermatophytosis nor anything else we could think of Substitution of niacin for the yeast solved the problem The other patient said that niacin made her hands and feet swell They were swollen and the substitution of yeast for niacin was followed by the disappearance of the swelling We have no explanation for these reactions unless they were on an allergic basis We noted in our clinic that most pellagrins have very bad teeth and few could afford adequate dentistry Excellent work has been done in the field of childhood dentistry by public health agencies For example the North Carolina State Board of Health holds free dental clinics for school children We believe that free dental clinics for adults unable to pay for adequate dental care would be a real advance in public health in those sections where such have not been established We do not know that the teeth of pellagrins are any worse than those of others in similar circumstances, but we advocate proper dental care for all so far as practicable

Rest is valuable in the treatment of pellagra It is probable that bed rest explains the clinical recovery of some patients on a pellagra producing diet However with niacin mild cases can be treated very successfully in ambulatory patients Severe cases should be put to bed

Constipation is treated best by enemas In cases with intractable diarrhea studies should be made for complicating intestinal infections such as the dysenteries, hookworm disease and other parasitic conditions, etc and these be treated appropriately Excluding these kaolin or kaolin with pectin may be given and in

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better as only 2 of 7 cases treated with it died, but dried stomach (ventriculin) in 10 gm doses daily plus hydrochloric acid was followed by recovery in all cases so treated Clinically moribund cases rapidly lost their edema fluid, the skin and mouth lesions healed, the diarrhea stopped, and recovery seemed complete in a week The authors do not state in what medium the dried stomach was given The present authors have not encountered pellagra in infancy, but when it occurs the above findings would suggest dried stomach, ventriculin, as the treatment of choice Certainly it should be tried, not only in infants but in all young children with pellagra, who do not respond promptly to niacin and perhaps in refractory adult cases, should such occur

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CHAPTER XIV

MYOSITIS

BY WALTER R. STEINER

TABLE OF CONTENTS

MYOSITIS

Myositis is inflammation of the muscles. The voluntary muscles alone are affected in all the varieties except the two known as dermatomyositis and polymyositis hemorrhagica when the heart muscle is implicated also. This involvement in the former however is found only rarely. Myositis has been long known as a primary or secondary disease. Many classifications have been introduced for it but that of Lorenz[29] seems at present more suited for clinical convenience. The secondary myositides which occur in pyemia, ulcerative endocarditis, actinomycosis, erysipelas, gonorrhea, pneumonia, typhoid fever and other infectious diseases are plainly of secondary origin and will be discussed under their appropriate headings. In tuberculosis the type seen generally is secondary and results from an extension of the diseased process from contiguous tissues. Hanke[1] in 1932 reported 55 instances of the primary form. For a further consideration of this form of tuberculosis see the paper of Milch[2] on so called primary tuberculosis. He adds 3 additional cases with one of his own.

PRIMARY SUPPURATIVE MYOSITIS

This sometimes is a single but generally a multiple muscle inflammation, mostly acute, of bacterial origin, presenting clinically the picture of

Pathology

Three varieties of suppurative myositis have been recognized (1) with large solitary abscesses in the muscles (2) with disseminated abscesses in the muscles and (3) with diffuse purulent infiltration in the muscles In the disease we are discussing most of the cases reported can be placed under the first heading While the skin and underlying tissues over the affected muscle or muscles appear normal the muscle shows extensive changes for it is dark red to grayish red in color densely infiltrated with serum and very friable while the abscess in the muscle contains a thick greenish yellow pus mixed with blood and tissue particles The walls of the abscess are lined with gray or yellowish gray necrotic fibers If the invasion is extensive only a few shreds of muscle may remain hanging from the sarcolemma sheath (Chassaignac s case) Microscopically the findings may vary being of a serous seropurulent or purulent character *Scriba thought the interstitial tissue was not altered but Miyake in all* the 14 cases he examined found the interstitial tissue much increased and infiltrated with mononuclear and polymorphonuclear cells Rarely the muscle fibers were completely replaced by this tissue The findings differ as to the extent of individual muscle changes Hyaline granular and fatty degeneration have been described by some investigators while one has encountered also vacuolar degeneration The muscle nuclei are somewhat increased and the sarcolemma sheaths are much thickened The bacteria are found in clumps near the wall of the abscess In advanced cases an extensive amount of granulation tissue is found with a new formation of muscle fibers from the proliferation of the muscle nuclei

Symptoms

A sudden onset generally is seen in a previously healthy individual beginning with a chill followed by fever Prodromal symptoms may how ever be noted such as *general malaise profuse perspiration anorexia* headache or pains in the extremities The pain is at first poorly defined but soon becomes localized in the affected muscles which reveal upon examination a tender indurated swelling This may be very painful on palpation There may be some edema also of the underlying tissues and extensive areas of erythema or ecchymoses may be noted Within four to ten days the swelling generally becomes softer and shows signs of fluctuation By incision the abscess is readily found but if such incision be delayed multiple abscesses may result with the final death of the patient Rarely the stage of induration ends in resolution The affection

an acute infectious disease which generally ends in suppuration The French first devoted particular attention to this disease which Foucault[3] described in 1869 Later it has appeared in other countries and seems most frequent in Japan In 1904 Miyake[4] states that 250 cases had been reported there

A tropical disease first described by Ziemann[5] in West Tropical Africa and named myositis purulenta tropica is possibly a variety of this affection although Walker[6] and other investigators consider the localization of the pyemic foci in the muscles to be due to filaria The evidence upon this point however is inconclusive More recently Sayers[7] has reported instances which did not go on to suppuration and were not caused by filaria

Etiology

Suard[8] who based his thesis on the 14 cases he collected from the literature first ascribed infection as the cause of this disease and later Scriba[9] and Brunon[10] were able to prove the correctness of this view by finding microorganisms in the pus from the muscle abscesses Various organisms of the pus producing type have been isolated so that Brunon[10] thinks the disease may result from any one of them Other investigators however find the staphylococcus pyogenes aureus in every instance Small infected wounds furuncles or acne pustules may serve as the original portals of entry and apparently the mucous membranes may also at times act in this capacity From these foci the bacteria are carried to the muscles by the blood stream so the affection is distinctly of septicopyemic origin The muscles may be made susceptible of invasion by trauma overexertion or hyperemia Brunon thought the muscles most used were more apt to be affected

Age — Age seems to have no relation to its appearance although it was formerly thought to be more frequent in children In Miyake s series of 32 cases 18 were under while 14 were over 25 years of age which is not in accord with the idea of a particular frequency in children as at first was thought to be the case

Sex — The sex also has no direct influence on this affection although it is seen more commonly in men as they are more subject to trauma or overexertion which are two important predisposing causes It is more common in the laboring classes

Season — The cases are most frequent according to Fujiy[11] when the laboring classes work in the fields and thus subject themselves to the predisposing causes of cold and fatigue

recognized until E. Wagner[12], Unverricht[13] and Hepp[14] almost simultaneously described it in 1887. Marcus and Weinstein[15] in 1935 reported a case and gave a thorough review of the literature. About 75 cases[16] fairly typical in type have been reported.

Etiology

The cause is as yet unknown. Many think it of infectious origin and microbes, vegetable and animal in character, have been found in the muscles and assigned as the causative factors of this disease. Unverricht considered the disease due to gregarines similar to canine gregarinosis. In this connection Theobald Smith[17] has made an interesting suggestion that the disease may be due to the invasion of the muscle by sarcosporidia from animals, especially the pig. These parasites on entering its aberrant host might not be present in sufficient numbers for histological recognition but might produce enough foreign protein to cause a multiple muscle inflammation with the other accompanying symptoms. Senator advanced a toxic theory, which at present has no supporters. Cold and fatigue may be exciting causes. As an established etiology is completely lacking, Hanger[18] thinks there are no grounds for considering this disease as a clinical entity, but he is the only one of the many writers who holds this view.

Distribution. — Cases have been reported in the United States, England, France and Germany.

Race. — The Anglo-Germanic race has contributed most of the cases with the Latin and Scandinavian races following second and third.

Seasons. — The time of year has no connection with the disease.

Sex. — The male sex slightly predominates in its distribution among the sexes. Most of the patients were in adult life but Lehmkuhl[19] collected in 19 8 16 cases in children, two being three years of age.

Pathology

By careful autopsies on at least 25 typical cases and a minute muscle examination in 15 more our knowledge reveals the findings to be limited to the muscles with the additional involvement of the spleen, which is both large and soft. Any or all of the muscles may be attacked. Lorenz has found that the cases in which the heart muscle is involved show a special tendency to relapses, although they may be mild or even abortive in type at onset.

The skin over the affected muscles is hard and does not pit on pres-

may involve one or many muscles If many muscles this form may be multiple from onset or begin as a single focus of infection which later becomes multiple Recurrences also must be borne in mind in two instances three and four months had elapsed before this was noted

Diagnosis

If the disease is seen from its onset there will be but little difficulty in a diagnosis Osteomyelitis may resemble it although the former generally spreads to surrounding tissues and not to other parts of the body by metastatic foci If in doubt a wide surgical incision will clear up the diagnosis if the abscess cavity is carefully palpated by the examining finger In pyemia there is no dense infiltration of the muscle or muscles invaded and no marked local disturbances

Prognosis

If seen early enough for the necessary surgical treatment the outcome is favorable In Miyake s series of 33 cases there was only one death Healing generally ensues after the abscess is emptied in from one to three months If surgical treatment is neglected the prognosis may be very grave from the formation of metastatic foci in other parts of the body Muscle atrophy may be observed upon the healing of the abscesses but usually there is no functional disturbance Severe contractures resulting from scar tissue which has replaced the loss of muscle substance is a very rare occurrence Pneumonia generally is a serious complication

Treatment

By the use of cold and other antiphlogistic means the muscle inflammation may subside without suppuration but generally such is not the case and the use of an early broad surgical incision should be employed to evacuate thoroughly the pus If contractures result after healing massage and various orthopedic measures should be utilized

Dermatomyositis

Dermatomyositis is an acute subacute or chronic disease a non suppurative form of myositis of unknown origin characterized generally by a gradual onset with vague and indefinite prodromata followed by edema dermatitis and a multiple muscle inflammation The disease was not

recognized until E Wagner[1] Unverricht[13] and Hepp[14] almost simultaneously described it in 1887 Marcus and Weinstein[15] in 1935 reported a case and gave a thorough review of the literature About 75 cases[16] fairly typical in type have been reported

Etiology

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By careful autopsies on at least 25 typical cases and a minute muscle examination in 15 more our knowledge reveals the findings to be limited *to the muscles with the additional involvement of the spleen which is* both large and soft Any or all of the muscles may be attacked Lorenz *has found that the cases in which the heart muscle is involved show a* special tendency to relapses although they may be mild or even abortive in type at onset

The skin over the affected muscles is hard and does not pit on pres

sure although slight edema usually is present On section the subcutaneous tissues show a firm edema and are generally infiltrated with a yellowish serous fluid The microscope reveals more extensive changes for the muscles are swollen and pale red or pale yellow in color They are also markedly infiltrated with serum and of variable consistency being either hard and firm or soft and boggy They are dull and opaque in appearance and may reveal hemorrhages in them occasionally The fibers are seen in all stages of degeneration being coarsely or finely granular hyaline wavy or occasionally fatty They may be normal in size atrophied or edematous Longitudinal or cross change of the fibers and vacuolar degeneration have been described as well as round cell infiltration in the perivascular connective tissue and to a lesser extent between the muscles In the more advanced cases the connective tissue may be much increased at the expense of the muscular tissue At autopsy bronchopneumonia was found as the terminal infection in seven instances of this disease

Symptoms

Those in the prime of life and in the most vigorous health are most susceptible to this disease The onset generally is gradual with various prodromal symptoms such as malaise anorexia or pains in the extremities which may be of several days to three weeks duration The pain is at first vague and accompanied by a rigidity in the extremities and back Soon it is more well defined in the muscles and different groups are successively attacked so that finally the whole musculature of the body may be implicated Subsequently the pains become much more severe of not only a spontaneous origin but also from active or passive movements The pain is drawing tearing or boring in type and in the most severe cases causes the patients to be helpless in bed The muscles usually are very tender on palpation and contractures have been observed in a few cases

Simultaneously with the fever edema appears and may spread over the entire body and extremities Usually it is first noted above the eyelids or other portions of the face and Oppenheim has likened the immobile cast countenance thus induced to alabaster The swelling is always observed in the extremities the proximal parts being especially prone to involvement while the wrist and ankle joints usually are spared The edema may be hard or soft in character and remains localized in the affected parts or spreads to surrounding areas It is not symmetrical in appearance

Dermatitis is an early symptom which is most protean in character as erythema a pseudo erysipelas an urticaria a roseola an eczema or an *inflammation resembling erythema nodosum* have been described It may spread gradually over the entire body or remain limited to the part first attacked Exceptionally it may occur late in the disease Its location *is almost always over the diseased muscles and it may disappear* without leaving a trace behind or a pigmentation may be seen resulting from its appearance Rarely the eruption may present successively two different types

Fever usually is of a moderate severity and soon noted It may be intermittent or remittent in type Profuse perspiration and an enlarged spleen usually accompany the other signs and symptoms Stomatitis and angina may be seen either at onset or late in the disease In four of Oppenheim s cases there was ulceration of the mucous membrane The muscles of respiration and deglutition are attacked frequently which explains the number of fatal cases due to bronchopneumonia or suffocation Moderate leucocytosis with a relative increase of the polymorphonuclears is seen most frequently but a leucopenia has been present occasionally Fiedler[20] Krohn[1] and others have reported an eosinophilia in Fiedler s cases as high as 76 per cent but this is an unusual find A mild anemia frequently is present The urine usually is normal but may contain albumin with hyaline and granular casts

Paresthesia as exhibited by the feeling of formication has been described by four different observers and peculiar cramp like pains in the later stages of the disease are of frequent occurrence The knee jerks and the electrical reactions are either normal or diminished

The disease in the subacute and chronic cases may show improvement alternating with relapses The duration of acute cases lasts from one or *two weeks to two months the subacute cases two to eight months* and the chronic forms from a year and a half to two years (Martini Lorenz[22])

Diagnosis

The following diseases present symptoms which resemble this disease (1) trichiniasis (2) neuromyositis (3) primary suppurative myositis and (4) syphilitic myositis In (1) the discovery of the trichinæ in the circulating blood the stools and the excised muscles as well as the blood findings in (2) the absence of a dermatitis and the marked nervous symptoms in (3) the presence of pus foci in the muscles and in (4) the Wassermann reaction with the patient s history generally will sufficiently

distinguish them from this disease In one case scleroderma was diagnosed while another later exhibited a typical example of this affection In scleroderma however the course of the malady generally is more chronic as Brock[3] has pointed out and fever commonly is absent Sclerodactylia and trophic ulcers with vasomotor disturbances usually are seen in this condition and not in dermatomyositis More thickening of the walls of the blood vessels more increase in fibrous tissue and less evidences of inflammation are observed in the former condition by microscopic examination

Prognosis

In 75 cases collected by Brock[3] 40 had a fatal outcome so the prognosis is grave as one would expect when it is known that all the muscles of the body may be involved including those of respiration and deglutition Death consequently may result from suffocation or bronchopneumonia Sixty five per cent of the patients died within two years of the onset but the disease has been fatal in eight days A relapse was observed two years after recovery in van Crevald s case

Treatment

By rest in bed the inflammation of the muscles may subside Oppenheim also recommends thermomassage at onset or later followed by massage gymnastic exercises and electrotherapy Pain is relieved by aspirin the salicylates or in the more severe cases by morphia It is important to keep up the patient s nutrition

POLYMYOSITIS HEMORRHAGICA

Polymyositis hemorrhagica is an acute subacute or chronic disease of unknown origin strongly resembling dermatomyositis but differing from it chiefly in the presence of a greater or less amount of interstitial hemorrhage between the muscles and the occurrence of circulatory symptoms caused by the implication of the cardiac muscle The disease was given a clinical existence by Lorenz who was able to find five cases one being a personal observation

Etiology — Unfortunately nothing definite as to the etiology of this affection is as yet known Bacteria (staphylococci) were found in two instances but one of them may have been the skin coccus which is found normally in the deeper layers of the skin Cold and fatigue and an

inflammatory condition of the tissues of the neck are other contributing factors which have been named in the published cases

The chief findings in the muscles vary from simple hemorrhages to extensive muscle degeneration and new connective tissue formation Lorenz has divided the changes into the acute and chronic types The intramuscular hemorrhages with destruction of the muscle fibers and muscle degeneration as described under dermatomyositis may be grouped here while in the chronic type new connective tissue is noted with blood pigment and markedly atrophic fibers

Symptoms —The symptoms are similar to those already described under dermatomyositis with the exception of the usual absence of prodromal symptoms The onset is more sudden and the fever less Pain is the first symptom complained of which is confined to a small area where a nodular tumor tender on palpation later develops The extremities generally are attacked first and the edema may vary greatly being as extensive as in dermatomyositis although generally it is distinctly more circumscribed and softer in consistency Different muscle groups may be involved gradually until the whole skeleton musculature is implicated

The skin may show a hemorrhagic or measly eruption with resulting pigmentation All of the cases save one have shown circulatory changes such as palpitation tachycardia arrhythmia or more rarely murmur Splenic enlargement is an inconstant symptom Bleeding from the intestines has been noted as well as attacks of epistaxis hematuria and profuse menstrual flow Nephritis is a frequent complication The disease generally is of several months duration

Diagnosis —The sudden onset with moderate fever characteristic skin eruption cardiac involvement and muscle findings will distinguish it readily from dermatomyositis

Prognosis —Four out of 10 in Thayer s list [4] recovered so the prognosis is grave as in dermatomyositis

Treatment —See Dermatomyositis

NEUROMYOSITIS

The term neuromyositis has been applied in a few instances to cases showing a myositis associated with a neuritis It is seen usually in alcoholics and is accompanied then by ataxia Probably it is not a disease per se but is seen when the two diseases coexist. Possibly it is an avitaminosis

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PRIMARY MYOSITIS FIBROSA

Primary myositis fibrosa is a single or multiple muscle inflammation mostly subacute or chronic which generally begins in the lower extremities and presents but slight constitutional symptoms Finally the muscles concerned are wholly or largely replaced by connective tissue with marked muscular atrophy resulting Burton Cowan and Miller[26] give an excellent description of the disease with references to the reported cases while more recently Schwab together with associate observers[6] and Ornsteen[27] have added two additional cases

Etiology — It probably has an independent existence although some have claimed it was secondary to infectious or rheumatic conditions No organisms have been found in connection with the disease nor does any sufficient etiological cause exist to explain it Age and sex seem to play no part in its incidence the youngest case being nine months and the oldest forty eight while its distribution among the sexes is about equal

Pathology — The muscles attacked are swollen and tumor like in appearance On palpation they may be firm and hard A dense edema may involve the skin and underlying tissues which does not pit on pressure If cut the muscles grate under the knife and show a white hard surface in the most involved areas but the less affected portions show reddish yellow spots which represent the remains of some of the muscle fibers Occasionally the connective tissue may replace them entirely In other portions the fibers are atrophied and show a granular or fatty degeneration Their cross striations have disappeared, but their longitudinal striations are more evident There is a relative increase of tendinous tissue at times noted Schwab and associated observers found a high grade of creatinuria in their case which may be attributed partly to the patient having also tuberculosis

Symptoms — Slight symptoms with a slow onset usually are the rule. The muscles of the lower extremities generally are the first involved and then only one muscle or a single group of muscles is attacked The pain in the muscles is the first symptom which quickly forces the patient to take to his bed Subsequently a rigidity of the muscles implicated with contractures is noted the flexors being especially liable to attack Eventually most of the voluntary muscles may be concerned The electrical reaction of the muscles may be reduced or be absent Disturbances of sensation are of very rare occurrence

Diagnosis — As Lorenz[12] has shown a positive diagnosis is impossible without histological examination The slight or total absence of pain on palpating a muscle in this disease is said to be characteristic as well as

the eventual hardening of the muscle involved and the cessation of the pains

Prognosis —The disease is of long duration and may remain stationary but generally a decided improvement eventually results

Treatment —Massage and electricity are of benefit in the disease if properly carried out but drugs have little value

Progressive Myositis Ossificans

Progressive myositis ossificans is a progressive inflammatory affection of the locomotor system of unknown origin characterized by the gradual formation of bony masses in the fasciæ muscles aponeuroses tendons ligaments and bones with resulting ankyloses of most of the articulations Freke[8] first described the disease in 1740 but it was not till Munchmeyer's paper[9] appeared in 1869 that it became a definite entity Since then about 175 instances of this malady have been reported Some of them are to be found in the side shows of circuses and in dime museums The name of this disease is unfortunate as there is no ossification of the muscles but an ossification of the fasciæ and of the intermuscular connective tissue as well as in the aponeuroses tendons ligaments and periosteum of bones

Etiology

It is frequently described as of congenital origin but the hereditary case which Burton Fanning[10] has reported was unique in the literature upon this disease until Gaster[1] reported a family in which the father and grandfather had the disease as well as three sons but the mother and the two daughters were free from it the transmission coming through the females as in hemophilia An ossifying predisposition or diathesis is the explanation of this congenital aberration of growth which is called into action by some exciting cause such as cold unsanitary surroundings trauma (either slight or severe) or single or many successive injuries It may be present however at birth Recent studies seem to show the disease may be connected in some way with rheumatism Two theories have been advanced as to the disease In the first the process of bone formation is considered to be of inflammatory origin while the second view regards the bony growth as due to tumor formation This last theory has much clinically to support it and is the more popular at present

Age —The disease usually is observed first in young persons although

rarely an example of it is found later in life The recorded instances give an earlier incidence in women than in men In Lorenz's list of 45 cases 38 were affected before the fifteenth year and 11 of them exhibited signs of the disease during the first year of life 16 between the first and fifth years and 11 between the ages of five and fifteen In Nutt's list[22] of 112 cases 102 started before the tenth year, although the 10 other cases started later in life

Sex — Males are attacked more frequently than females the ratio being variously given as four or five to one but in Mair's[23] series of 66 cases the ratio was two and one half to one In Weil and Nissim's[24] series of 50 cases 38 were men and 12 were women Pincus explains this as due to obstetrical traumatism and claims this happens more frequently in boys than girls as they are better developed

Race — The Anglo Germanic race has furnished most of the instances while the Latin and Scandinavian races report isolated cases

Pathology

The pathology of the implicated muscle was first described in 1844 by Hawkins[3] and thirteen years later it was again investigated by Minkewitsch[36] but the disease was not made a definite entity until Munchmeyer's[9] classic article appeared in 1869 in which he tersely described the process of bone formation in the muscles He recognized three stages of the disease which have subsequently been adopted by other writers (1) stage of embryonic infiltration (2) stage of connective tissue induration and (3) stage of ossification In the first stage the skin and subcutaneous tissue may seem normal but the underlying muscle if affected is much swollen and edematous from an extensive infiltration of the intramuscular and intermuscular connective tissue This infiltration results from the formation and proliferation of embryonic connective tissue especially about the blood vessels In the second stage the embryonic tissue becomes organized forms adult connective tissue which after proliferating contracts and finally becomes a hard fibrous mass On section it has the appearance of a fibroma with the remaining muscle fibers appearing as red striations in the white background Fatty waxy and granular degenerations of the fibers have been noted as well as their complete destruction The changes are more marked as the center of the hard white mass is reached The sarcolemma nuclei may be markedly increased as well as the intermuscular connective tissue which generally is very rich in cells of the fusiform to the large polymorphous type The latter generally contain many karyokinetic figures Cells resembling car

tilage cells without capsules are observed also which later appear to produce hyaline cartilage Towards the centers of these fibrous masses spaces are seen which are the osteoid trabeculae in which formative cells are found which later represent osteoblasts and bone corpuscles When calcification takes place the parts enclosed by the trabeculæ become bone marrow and compact and spongy bone is formed when ossification ensues New bone is formed also in the fasciæ ligaments tendons and preexisting bones in a similar manner It is of the fibrous cartilaginous or periosteal type and resembles true bone in every respect In 1927 Ipponsugi[37] published an unusually complete pathological study of this disease He found calcified masses but no bone formation in the brain both kidneys the mucous membrane of the colon tracheal cartilage walls of the spleen and in a large amount in the pineal gland Friedberg and Salmann regard the disease as a primary parenchymatous muscle inflammation but Lexer who examined also the sections in the latter case considered the fascia to be the first site of a hyperplastic process Ipponsugi[37] Rosenstirn[38] Mair[33] and all recent observers consider the process to involve the mesoblast the connective tissue structures which possess the potential function of osteogenesis There is also present a disorder of calcium metabolism of an unknown etiology Wilkins Regen and Carpenter[39] recently have reported the phosphatase activity of muscles in the preossification stage as 800 to 1 600 times that of normal muscle and several times that of normal bone The activity of heterotropic bone was much greater than that of normal bone

Symptoms

The symptoms vary in the beginning and frequently the cases are diagnosed as rheumatism until the stage of bone formation is reached Some of the cases may begin so insidiously that signs of muscle inflammation may be absent In typical cases however a myositis is present which causes the muscle affected to present a swelling of a firm doughy consistency Pain may be localized here or be radiating in character On inspection there is edema of the overlying tissues with some redness of the skin Slight fever usually is present After a few days or longer depending upon the severity of the process the symptoms vanish but the implicated muscle remains indurated forming finally a hard tumor like mass which eventually may show bony deposits or remain as a fibrous tumor Occasionally the mass disappears with resulting fibrous degeneration of the muscles and more rarely the affected muscle is restored to its former healthy state

This process of bone formation generally requires from two to eight months and may be observed in the whole muscle in its fleshy portions or in its tendons These bony changes usually are painless but spontaneous pains especially at night are observed at times The muscles of the back and neck are generally the first involved while those of the upper and lower extremities and finally of the face follow in the order named The ossification of the cervical ligaments and of the neck muscles explains the flexion forward of the head and the fixed position of the neck The ossification of the ligaments fasciæ and muscles of the back varies greatly If localized in a muscle the bony deposit may feel like a freely movable irregular plate but often the ossification has extended further and has anchored the muscles firmly to the skeleton These bony masses have been likened to the ramifications of coral (Copping) to a geographical map of a mountainous region (Brennsohn) or to a stag s antlers (Minkewitsch) The disease may progress no further than the stage of connective tissue induration and in some instances when the stage of ossification has been reached the bony lesions may disappear entirely

Eventually the vertebral column becomes fixed and a scoliosis may be observed which may be so marked that the lower rib may touch the iliac crest A kyphosis is seen much more rarely If the pectorals and latissimus dorsi are involved the arms are fixed rigidly on the thorax which has been described occasionally as a bony coat of mail The disease as it progresses implicates more and more muscles and fixes the corresponding joints in the manner above described the upper extremities usually being involved earlier than the lower but eventually both show marked contractures Finally the hips are slightly flexed at the pelvis and the arms are fixed at the shoulder and flexed at the elbow By this posture with the forward projection of the head the patients exhibit a precipitous gait The forearms hands legs and feet are attacked only rarely When the temporals masseters and pterygoids are attacked the patients are unable to move their lower jaws so that the resulting difficulty in feeding is only overcome by removing some teeth or a portion of the alveolar process of the lower jaw

Besides the above symptoms the presence of exostoses is noted frequently They are generally described as on the internal surface of the arm the anterior aspect of the tibia the upper portion of the fibula the ribs or where the long bones approach the skin They have been found also on the frontal bones and the phalanges of the fingers They may later disappear In about seventy five per cent of the cases a peculiar deformity of the great toes and thumbs has been observed Occasionally the little fingers have been involved This peculiarity was first described

by Gerber but Helferich later directed more particular attention to it Its origin is due to the dwarfing in the growth of the metatarsal and metacarpal bones with the subsequent ankylosis of the interphalangeal joint Before the introduction of the x ray one phalanx was considered absent The great toes generally are directed outward and frequently lie under the second toes giving rise to the deformity of hallux valgus In Michelsohn s[10] patient the deformity of the toes was seen at birth but that of the thumbs was not detected until the seventh year For an excellent consideration of this deformity see Jungling[41] who reports thirty examples Other deformities such as absence of some muscles and atrophy of the testicles and scrotum have been described in isolated instances

Diagnosis

In advanced cases a diagnosis is possible at a glance but in the early cases the age of the patient the early sites of the bony deposits the pro gressive march of the disease the exostoses and the microdactylia are important factors in differentiating this from other diseases Multiple exostoses have been confused at times with this malady but their arrest in development past the age of twenty their bony character from the beginning and the absence of primary muscle involvement will distinguish them readily

Prognosis

The progressive character of the disease should always be borne in mind although a cessation of symptoms may alternate with relapses and long intervals such as 16 or even 23 years may be noted in which the progress of the disease may seem to have been checked Eventually the patients become helpless and bedridden Bedsores and abscesses about the bony deposits may make their lives truly most miserable until their death may ensue from pyemia or some intercurrent infection such as tuberculosis or pneumonia Suffocation may intervene from the limita tion of costal breathing and the onset of edema of the glottis

Treatment

Medical treatment is most unsatisfactory The surgical removal of the bony deposits has been attempted in a number of instances with a resulting recurrence of these deposits at the site of removal in every in stance If the lower jaw is fixed however operative measures are justi

fiable. Precautions against trauma and cold may somewhat check the spread of these bony deposits.

As Guyatt, Kay and Branion[4] found that beryllium carbonate caused in the rat a marked reduction in the inorganic phosphorus of the serum, Tutunjian and Kegerreis[43] gave their patient this drug first at the rate of three grams per day and later six grams per day, a total of 200 grams being given without untoward symptoms. Unfortunately no apparent change in the serum calcium was observed, but possibly this drug should have been administered before the full development of the osseous system.

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